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THEORETICAL MECHANISMS OF IMMUNOLOGICAL TOLERANCE

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IMMUNOLOGICAL tolerance, or the failure of the organism to react immunologically to stimuli, which under other circumstances are antigenic, has attracted considerable attention in recent years in the fields of embryology and general biology, as well as in immunology. Classical concepts of antibody formation seem largely inadequate to deal with the newly discovered facts, but despite this, comparatively few of the active workers in the field have ventured any general theoretical interpretation of the phenomenon. Although some may have believed that it is premature to attempt any unitary scheme to account for all the known facts,[45] the heuristic value of such attempts is well shown by the experimental work stimulated by the original "self-marker" hypothesis of Burnet and Fenner.[11]

The following review deals briefly with the more important theories which have been advanced to explain the phenomena of natural and acquired immunological tolerance, and concludes with a short consideration of a new hypothesis.

It will be assumed that the reader is conversant with the salient facts, access to which is possible through a number of reviews[6,10,39,40,45] and the published proceedings of several conferences. Other references cited in this review are selected for their relevance to the particular theoretical points under discussion, and no attempt is made to allocate priority.

FACTS TO BE EXPLAINED BY ANY THEORY OF IMMUNOLOGICAL TOLERANCE

Burnet and Fenner[11] and Burnet[8] have listed a number of points which any comprehensive theory of antibody formation must cover. In addition

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to these, certain basic facts of immunological tolerance must be accounted for in any general formulation. The following facts are to be found in the general references given above, or in the specific authorities cited.

1. Homografts between normal adults do not usually "take" permanently, except between identical twins or members of highly inbred strains. Even in inbred strains, grafts from a male donor are not well tolerated by a female host.[3]

2. After rejection of a homograft, a second homograft from the same donor is rejected more rapidly.[3]

3. Under suitable conditions, homografts (sometimes even heterografts) take permanently in immature (embryonic or newborn) animals, and subsequent grafts from the same donor (or from a member of the donor's inbred strain) also take. This "acquired tolerance" is highly species-specific or strain-specific, but is not organ-specific (i.e. early grafting from a particular donor strain will not usually permit later grafting from another strain, but early grafting of one organ or tissue will facilitate later grafting of a different organ or tissue from the same donor strain).[6]

4. Acquired tolerance is not an all-or-none phenomenon; various degrees of prolongation of life of a graft may be achieved.[3]

5. Organisms do not normally form antibodies to their own tissues or antigens. Auto-antibody reactions can be induced by the injection of antigens which do not normally reach the antibody-forming cells (e.g. lens protein, sperm, thyroid colloid), or by the injection of the animal's own tissues plus certain adjuvants.[40]

6. The homograft reaction is not simply an antigen-antibody reaction mediated by classical serum antibodies, because access of host cells to the graft is usually necessary for rejection to occur. Some central immunological mechanism is involved however, probably implicating either "cell-bound" or "incomplete" antibodies,[1,27] and homograft tolerance is a specific *central immunological failure* of response.[6]

7. The homograft reaction is initiated by the escape of antigens from the graft. These antigens are continually being released even by tolerated grafts, and presumably also by normal tissues.[42]

8. Immunity to a graft can be transmitted to an animal with specific acquired tolerance by the grafting of lymph node cells from an immune animal of the host's inbred strain, or more slowly by the grafting of lymph node cells from a normal animal of the host strain.[41,42]

9. Homograft antigenic differences between inbred strains of mice are attributable to "histocompatibility genes" following normal Mendelian rules.[53,54]

10. Injection of small or moderate amounts of non-living antigenic material into embryonic or newborn animals does not usually result in an antibody response, and later antibody response to an antigenic challenge with the same antigen is diminished for a period which is a function of the

original dose. Repeated injections of the antigen from birth onwards can prevent an antibody response apparently indefinitely. Persistent tolerance to both non-living antigens and to foreign cells appears to depend on the continued presence of the antigen.[2,12,13,15,22,29,30,31,43,52,61,64]

11. Injections of *large* quantities of normally antigenic material into adult animals has been shown in some cases not to result in the formation of demonstrable antibody, contrary to the response to small or moderate doses.[21,22,26]

The phenomena of "immunological paralysis" and "enhancement" and certain facts and observations possibly relevant to theories of immunological tolerance are discussed below in their appropriate places.

THEORIES OF TOLERANCE SHOWING THE INFLUENCE OF TELEOLOGY

The absence of auto-immune reactions in normal individuals has attracted the interest of immunologists from early days, but such absence seemed natural and seemed to require no mechanism. Many biologists, therefore, accepted without question Ehrlich's principle of *"horror autotoxicus"*, which expressed the concept that

> ". . . no living organism would be capable of producing—or would ***dare*** to produce, if you wish—an antibody against constituents of its own body, for this would be incompatible with life. . . ."[63]

Ehrlich, himself, used teleology consciously and deliberately, but managed to avoid its pitfalls. His teleology is expressed by his view of "horror autotoxicus" as a *"zweckmässigen* Regulationsvorgang", and by his statement that in human pathology it would be

> ". . . in höchstem Grade *dysteleologisch,* wenn unter diesen Umständen sich Eigengifte der Parenchyme, Autotoxine, bilden würden. . . ." (Italics ours).[28]

Despite this teleological approach, Ehrlich recognized that to avoid harmful production of antibodies the organism must possess

> ". . . certain regulating contrivances, the explanation of which would be of the highest interest. . . ."[24]

His investigations seemed to show that ". . . either the disappearance of receptors or the presence of auto-antitoxins is foremost among these contrivances."[25]

Ehrlich was unable to demonstrate the postulated auto-antitoxins. To understand what he meant by "receptors" would require an exposition of his "side-chain" theory of immunity, which cannot be given here.[63] Let it suffice to say that his interpretation of immunological tolerance (although he did not use this term) is formally similar to one propounded by Talmage[58] and by Burnet[9,10] which is criticized below.

Some other biologists have also approached the subject of immunological

tolerance in a (probably unconsciously) teleological way, but have not always been as successful as Ehrlich in avoiding the pitfall of regarding teleological explanations as being equivalent to causal mechanisms.

Thus Medawar in explaining why auto-immune reactions do not commonly occur, says that antibody-forming cells

> ". . . could hardly be expected to react upon ingredients of the body which are also represented in themselves. This presumably debars the chromosomal apparatus, the enzymes of the cyclophorase and glycolytic systems with their associated structures, and indeed anything that we may expect to find in antibody-forming cells as well as in the other cells of the same body."[40]

Now it is known that many agents (narcotics, curare, etc.) have very different effects if applied to the exterior of cells or if injected into them[19] and there seems no *a priori* reason why a failure to form antibodies against a substance inside a cell should necessarily imply an inability to react to a similar *external* compound. The existence of distinct intracellular compartments extends the argument. It is difficult to see why the mere physical presence of intranuclear chromosomes should prevent an antibody response to a phagocytosed mass of nucleic acid in some cytoplasmic vacuole. Even if cells were to be regarded as simple bags of enzymes without internal organization, the failure of antibody-forming cells to form antibodies to their own cytoplasmic constituents would be a puzzle in its own right, rather than an explanation for a failure to respond to extrinsic antigens. This explanation of Medawar's thus reduces itself to a repetition of the "horror autotoxicus" concept, applied at a cellular level.

To account for the failure of antibody-forming cells to form antibodies against antigens which reach them from other cells of the body, and which are not present in the antibody-forming cells themselves, Medawar suggests simply that

> ". . . autoantibodies cannot be formed against substances to which antibody-forming cells are exposed during the course of normal development. . . ."[40]

This is at best a statement of fact, and not an explanation.

Voisin *et al.* take a similar stand to that of Medawar. They emphasize that

> ". . . the desoxyribonucleic acid-ribonucleic acid (DNA-RNA) system, which depends directly upon the chromosomal constitution of the cell and is thus strictly and completely determined by the genetic constitution of its parental ovum and spermatozoon, will not normally build proteins foreign to the organism. It seems difficult to admit that this synthesizing mechanism can build proteins that in turn, can induce the same mechanism to build antibodies against them. Consequently it is unlikely that normal 'standard' proteins can be autoantigenic regardless of any question of specific 'naturally acquired' tolerance. . . ."[60]

In accordance with this view, they found that the autoantigens of spermatozoa were probably non-protein in nature.

Little comment on the above concept is called for, except that it is essentially a version of the "horror autotoxicus" principle. One may also note in passing that complex non-protein substances found in organisms are presumably, like proteins, gene-determined; it is difficult to understand why such substances should be capable of inducing auto-antibody formation, if proteins are unable to do so.

THE "SELF-MARKER" HYPOTHESIS

Burnet and Fenner found it

> ". . . quite inconceivable that every complex molecule in a red cell or a lymphocyte should be so labeled that it can be recognized as autologous by every macrophage of the body and therefore provoke no antibody response."[11]

They suggested that only a limited number of "marker components" need be postulated, to which the intracellular enzyme systems of the macrophage cells would become adapted during embryonic life. The adapted enzyme, which would become stabilized as part of the inheritable structure of the cells, would be capable of specifically uniting with and initiating the destruction of such a component, without the formation of antibody. Antigens in general were visualized as ". . . substances of the same chemical nature as the marker components but of different molecular configuration."[11]

A weakness of the theory is the postulate that the enzyme adapted to a particular self-marker would become stabilized and part of the inheritable structure of the cell and its descendants (i.e. the cell clone). This fails to account for the fact (discussed more fully below) that in at least a number of known cases, continued acquired tolerance to a foreign antigen has been shown to depend on the continued presence of the antigen.

The self-marker theory appears to predict that

> ". . . one essential distinction between a potential antigen which is effective and one which is not lies in a difference in their intracellular fates—even if the difference be only that they are destroyed at significantly different rates."[33]

Humphrey, who supports the self-marker theory, quotes evidence that the intracellular fate of heterologous protein is essentially similar to that of homologous protein, but nevertheless insists that there must be some difference between the two. The only favorable evidence which he educes is that of McMaster et al., who demonstrated traces of antigenic foreign protein in the livers of mice several months after injection. However, traces of potentially antigenic material may remain in the tissues for prolonged periods without inducing demonstrable antibody formation[26,52] so that one cannot accept persistence in the tissues as being the only determining factor in antigenicity.

Burnet and Fenner[11] do not make it clear how a limited number of "self-markers" could affect the antibody response to the large number of potential antigens resulting from the breakdown or metabolism of cells. Self-markers could only have such an effect if all potential antigens were at all times

intimately associated with one or more self-markers. Consequently every complex molecule found in cells, supposedly non-antigenic by virtue of close association with a self-marker, would be antigenic if injected into the animal of origin in purified form. There is no evidence which substantiates this occurrence. The only escape from this dilemma is the extension of the self-marker concept to include all potential antigens, but such an extension would of course remove the initial premise of the hypothesis, and would be regarded by Burnet and Fenner as "quite inconceivable".

A treatment of the tolerance problem which is in some respects similar to the self-marker concept is that of Schultz,[47] who compares the state of acquired tolerance with one of the alternative cytoplasmic states of *Paramecium*. A *Paramecium* of a given genetic constitution manifests one of a variety of alternative antigenic serotypes, the particular serotype manifested depending on a number of factors present at the time the pattern of antigen synthesis is set. Schultz interprets acquired tolerance in mammals as being due to an environmental shock coming

> ". . . from the foreign antigens of the implant, which would be presumed to change the cytoplasmic state of the differentiating cell from a condition reactive to the foreign antigen to one in which the mature cell no longer responds by the synthesis of antibodies."

Apart from leaving the physical nature of the "environmental shock" and the "cytoplasmic state" undefined, this hypothesis has the weakness, in common with that of Burnet and Fenner, of not explaining the necessity for the continued presence of antigen for continued tolerance.

IMMUNOLOGICAL PARALYSIS AS A MECHANISM FOR IMMUNOLOGICAL TOLERANCE

Felton showed that relatively large doses of pneumococcal polysaccharide would not evoke antibody formation in injected mice, and would actually inhibit an antibody response to a later small (normally immunizing) dose. The polysaccharide was demonstrable in the liver, spleen and kidney of these "immunologically paralyzed" animals for prolonged periods. Felton explained the phenomenon in the following way:

> ". . . the facts that antibodies are synthesized in the reticuloendothelial cells and that the polysaccharide is found in nearly all the cells of immunologically paralyzed animals, point to the possibility, that with an appropriate dosage, a given antigen is so firmly attached to cell substances that it is no longer free to act as an antigen."[26]

The effect of the long persistence of the polysaccharide in the tissues would be ". . . simply to absorb out antibody as fast as it may be produced."[45]

Wiener applied the phenomenon in a theory of immunological tolerance:

> "The relative inability of the body to form antibodies against its own constituents is now ascribed to the phenomenon of 'immunologic paralysis'. For

> antibody formation to occur, the antigen must reach the antibody-forming cells in doses falling within a certain optimal range; if excessive amounts of antigen are present, the saturated antibody-forming cells cannot react."[62]

Why cells should fail to respond to a large dose of antigen is not explained by Wiener, and his interpretation of immunological tolerance further fails to account for the different response to a foreign antigen of an embryo and an adult.

It should be noted that Wiener's interpretation of immunological paralysis as being due to a failure of the antibody-forming cells to respond to an overwhelming dose of antigen, differs from the view of Felton and of Owen, who suppose that the cells are not unreactive, but that any antibody formed is immediately absorbed by an excess of antigen. It may be that both factors play a part.[5,22]

Work which it is convenient to mention at this stage is that of Taliaferro and Taliaferro who found that antibody-forming cells in the rabbit under certain conditions failed to produce antibody. They distinguished between the

> ". . . inactive phase during which a site resumes antibody formation upon further antigenic stimulation and the refractory phase during which antibody formation is not resumed in spite of continuous antigenic stimulation."[57]

The refractory phase was attributed to a temporary absence of anabolic intermediates acting as a limiting factor, and a possible relevance to persistent acquired immunological tolerance (which had not then been demonstrated) was not discussed by the authors. It is also not clear that the antibody-inhibition under the circumstances of their experiment was antigen-specific, so that it is by no means certain that there is a relationship between this type of non-reactivity on the one hand, and the highly specific immunological tolerance and immunological paralysis on the other.

CLONAL SELECTION THEORIES

Ehrlich's sidechain theory postulated the presence of cellular "sidechains" or "receptors", which were able to combine specifically with various circulating molecules. Produced in excess as an indirect result of combination with foreign molecules, the receptors were supposed to be released by the cell, and circulate as serum antibodies. The phenomenon of "horror autotoxicus" was explained by an absence of receptors able to react with the organism's own constituents. Similarly, some modern attempts to explain immunological tolerance have depended on the postulated elimination during embryonic life of those antibodies able to react with autologous antigens, or on the elimination of particular cell clones responsible for the production of such antibodies. The prototype of these theories is that of Jerne;[34] modifications have been presented by Talmage and Burnet.[9,10]

Jerne postulates that globulin molecules are

> ". . . continuously being synthesized in an enormous variety of different configurations. Among the population of circulating globulin molecules there will, spontaneously, be fractions possessing affinity toward any antigen to which the animal can respond."[34]

Foreign antigens in the blood or lymph will attach selectively to those molecules having the complementary surface configuration, and on being engulfed by a phagocytic cell will thus introduce the bound globulin into the cell. Once in the cell, the antigen plays no further role, but the globulin in some way stimulates the production by the cell of molecules identical to itself. In this way, increased production of the appropriate antibody would result. Normal globulins might be synthesized by an unselective reproduction of circulating globulin, resulting from a mechanism by which a small fraction of the circulating globulin could enter the appropriate lymphoid cells. Tolerance of endogenous antigens is accounted for in the following way: a spontaneous production of globulin molecules in the embryo is postulated. If

> ". . . this small spontaneous production of globulin took place mainly in embryonic and early life, before the much larger body of cells later engaged in maintaining the composition of the circulating globulin by reproduction had started to function, the early removal of a specific fraction of molecules might lead to the permanent disappearance of this type of specificity. Such a mechanism could explain the absence in the blood of specific globulin against antigens of the organism itself, since such globulin molecules, if spontaneously produced, would be removed by attachment to the auto-antigens and would no longer be available for reproduction."[34]

Jerne's theory satisfactorily accounts for the continued production of antibody after the elimination of antigen from the body. The gradual improvement in the quality of antibody produced during continued antigenic stimulation is explained by an occasional molecule of antibody being accidentally produced with an improved "fit", complementary to the antigen. Such a molecule of antibody will successfully compete for molecules of antigen, and will hence have a selective advantage over other molecules of globulin. The "secondary response" is accounted for by the antigen injected on the second occasion encountering a larger concentration of specific antibody than was present at the time of the first injection.

Talmage[58] modified the concept of clonal selection, by applying the selection to the antibody-producing cells rather than to circulating antibody. According to this hypothesis, ". . . only those cells are selected for multiplication whose synthesized product has affinity to the antigen injected."

Three pieces of evidence were regarded as bearing on this theory:

(a) The time taken for sensitization of an animal for the maximum anamnestic response is usually thirty days or more, suggesting multiplication of cells rather than the much more rapid process of multiplication of subcellular units, which may be important in the primary response.

(b) Sensitization once established persists for a long time, suggesting persistence of an already established cell type. Talmage suggests that:

> "It might be expected that a multipotential cell would revert to the presensitized state after a few cell divisions performed in the absence of antigen."

(c) The protein produced by rapidly reproducing myeloma cells has been considered to be remarkably homogeneous. Talmage quotes Putnam as suggesting that

> ". . . in an individual case there is massive production of one globulin randomly selected from the family of normal globulins."

Burnet has elaborated Talmage's scheme. He postulates that amongst the plasma-globulins are

> ". . . molecules with reactive sites which can correspond probably with varying degrees of precision to all, or virtually all, the antigenic determinants that occur in biological material other than that characteristic of the body itself. Each type of pattern is a specific product of a clone of mesenchymal cells and it is the essence of the hypothesis that each cell automatically has available on its surface representative reactive sites equivalent to those of the globulin they produce. . . . It is assumed that when an antigen enters the blood or tissue fluids it will attach to the surface of any lymphocyte carrying reactive sites which correspond to one of its antigenic determinants. . . . It is postulated that when antigen-natural antibody contact takes place on the surface of a lymphocyte the cell is activated to settle in an appropriate tissue, spleen, lymphnode or local inflammatory accumulation, and there undergo proliferation to produce a variety of descendants. In this way preferential proliferation will be initiated of all those clones whose reactive sites correspond to the antigenic determinants on the antigen used. . . . The net result will be a change in the composition of the globulin molecule population to give an excess of molecules capable of reacting with the antigen, in other words the serum will now take on the qualities of specific antibody. The increase in the number of circulating lymphocytes of the clones concerned will also ensure that the response to a subsequent entry of the same antigen will be extensive and rapid, i.e. a secondary type immunological response will occur."[9]

Burnet points out that the theory requires

> ". . . at some stage in early embryonic development a genetic process for which there is no available precedent. In some way we have to picture a 'randomization' of the coding responsible for part of the specification of gamma globulin molecules, so that after several cell generations in early mesenchymal cells there are specifications in the genomes for virtually every variant that can exist as a gamma globulin molecule. This must then be followed by a phase in which the randomly developed specification is stabilized and transferred as such to descendant cells. At this stage, again following Jerne, any clones of cells which carry reactive sites corresponding to body determinants will be eliminated. The necrotic effect of tuberculin on sensitized fibroblasts might be taken as a crude analogue of the process by which clones with unwanted reactivity can be eliminated in the late embryonic period with the concomitant development of immune tolerance."[9]

According to Burnet, his theory is superior to Jerne's in ". . . its capacity to cover homograft and related types of immunity as well as the production of classical antibody. . . ." On the other hand, Jerne's scheme accounts for

the improvement in quality of antibody with time in a more satisfactory manner than does Burnet's: natural selection would operate in both schemes, but might be expected to apply to minor deviations of protein synthesis more rapidly than to mutations of relatively stable cell clones.

Both types of natural selection theory appear to the reviewer to share a serious defect in that both seem to imply that immunological tolerance, once established, should persist indefinitely. Now there is considerable evidence indicating that, at least in some cases, continued acquired tolerance is dependent on the continued presence in the organism of the antigen. While persistently acquired tolerance to living cells or viruses has been produced by numerous workers, tolerance to cell-free or non-living antigens appears in general to be transitory. Without going into details, one may say that single injections of non-living antigens into embryos or newborns has not usually induced acquired tolerance.[2,12,30,61] In those cases where tolerance *has* been induced by injections of non-living antigens, repeated courses of injections were given, or the continued presence of antigen for the duration of the non-reactivity could not be excluded.[15,16,22,29,30,36,43,52,64]

For example, Wolfe et al.,[64] giving bovine serum albumin to newborn chicks, found that the duration of tolerance depended on the size of the original dose. Smith[52] gave injections of bovine serum albumin to newborn rabbits, and also found that the duration of immunological non-reactivity was a function of the initial dose. Initial doses of albumin of up to 100 mgm were sufficient to cause tolerance lasting at least six months in some rabbits. Smith concluded that an ". . . interpretation consistent with the data is that persisting antigen is related to maintenance of tolerance."[52]

It therefore appears probable that in some way the continued presence of antigen, administered under particular conditions, is necessary for the persistence of specific tolerance. The theory of clonal selection, which visualizes a rather static mechanism of immunological tolerance, appears to the reviewer not to account for this.

In an elaboration of the theory, Burnet[10] makes a number of new assumptions which must be considered.

Burnet now postulates that his clones of antibody-forming cells undergo frequent minor mutations even in the adult. The

> ". . . combination of frequent minor mutation and a highly effective selective process would rapidly improve the accuracy of the complementary relationship to new antigenic determinants."

According to Burnet:

> "All that is demanded of the primary differentiation or randomization of pattern is that a sufficient number of clones are produced to provide sites with *close enough* fit to all possible antigenic determinants to allow some reaction. As long as it is possible by directed protein synthesis to secure a better fit, it is legitimate to look to minor somatic mutation to allow its emergence."

Further, he writes:

> "As in every other evolutionary situation, the occurrence of neutral or deleterious mutations is quite unimportant, no matter how frequently it occurs. It is only the mutant which finds its opportunity to proliferate when the appropriate antigen is in the internal environment that is significant in changing the balance of the mesenchymal clones within the body."

To explain the results of Smith, referred to above, Burnet assumes a form of inhibition by antigen:

> "Under these circumstances so long as an appropriate number of antigenic determinants are in contact with a cell, the cell is rendered dormant in two senses: (a) it is incapable of developing into a plasma cell and producing antibody and (b) it remains at the same stage of immaturity as it was at the time of first contact with antigen."[52]

According to this interpretation, mesenchymal cells at birth react differently from adult cells due to immaturity. This explanation therefore does not cover the case of mutations of *adult* cells giving rise to autoantibody-producing clones.

Burnet recognizes this, and admits that:

> "A homeostatic mechanism must be postulated to allow, under favourable conditions, the extinction of mutant clones reacting with normal constituents of the internal environment. Presumably this consists of inhibition by excessive stimulation. . . ."

A suggested mechanism by which this homeostasis could be achieved, involves the assumption that on contact with an antigenic determinant, a mature lymphocyte will undergo ". . . a process of what might be called rejuvenation to the 'primitive stem cell' phase. . . ." followed by a change in its reactivity to:

> ". . . a more and more immature type, that is, that at a certain stage, probably just before proliferation is well established, the cell can be destroyed by a second contact with the determinant. . . ."

This postulated homeostatic mechanism seems contrary to certain experimental evidence: it is known that lymph node cells from an adult of one strain of inbred mice, when grafted into an x-rayed adult of another strain, frequently produce antibodies against the host.[59] This shows that in adults the level of circulating host-specific antigen is insufficient to inhibit or destroy antibody-forming cells *with no previous history of contact with the antigen.* Thus these cells do not appear to undergo the period of embryonic sensitivity to antigen postulated by Burnet.

Burnet's original clonal selection theory[9] has thus already been watered down by making the "stabilized" clones highly mutable, and by extending "embryonic" reactivity into adult life. If one further accepts some supplementary mechanism whereby under specified circumstances continued presence of antigen inhibits the formation of the corresponding antibody, the entire postulate of clonal selection becomes redundant, because the sup-

plementary mechanism could itself account for all the known facts of immunological tolerance.

Support for the clonal selection theory stemming from evidence other than the facts of immunological tolerance, has not been wholly convincing. For example, Talmage's interpretation of the globulin produced by patients suffering from myeloma as being randomly selected from the family of *normal* globulins (which do not react with the organism's own antigens), does not accord well with the apparent auto-antibody element of this disease.[35]

THEORY OF CINADER AND DUBERT

Cinader and Dubert postulated that immune tolerance to a particular antigen is due to the retention of the antigen

> ". . . in some locus, in the cell of the young animal, not accessible to antigen in the adult, and that this antigen combines with antibody formed, thereby preventing its release. The resulting accumulation of antibody within the cells would inhibit further synthesis of antibody."[15]

To test this hypothesis, they investigated the response of rabbits to injections of human albumin (HA) and a slightly modified antigen (diazotized human albumin, DHA). Intraperitoneal injections of HA were given to new-born rabbits, and repeated courses of injections were given at nine to ten weeks and at three to four months. In contrast with controls not given a first course of injections at birth, the experimental animals failed to produce antibody in response to the later courses of injections.

Normal rabbits responded to an injection of DHA by production of some antibody molecules similar to those formed in response to HA (and which could therefore be removed by absorption with HA in vitro), and also some antibody molecules specially adapted to the diazo group. The similarity of HA and DHA was recognized by the antibody-forming mechanism to the extent of producing a secondary response to HA when DHA had provided the primary stimulus.

Injections ". . . with DHA of animals injected with HA at birth did not produce an antibody to DHA in the majority of rabbits; the animals which formed an antibody to DHA also formed an antibody to HA. The HA antibody was of very low avidity."

One rabbit was originally tolerant of HA, and was rendered non-tolerant by injections of DHA. The evolution of antibody properties in response to DHA displayed by this rabbit was considered

> ". . . consistent with the production first of an antibody to DHA, cross-reacting weakly with HA and then of an antibody with a wider specificity, slowly evolving in the course of repeated immunizations until the antibody-forming mechanism is finally able to respond directly to the cross-reacting antigen."

Two other animals which were HA-tolerant formed antibody in response to DHA, and

> ". . . after further injections with DHA, the sera of both these animals were able to agglutinate HA-sensitized cells as well as DHA-sensitized cells. Both sera differed from those of the controls immunized with DHA, in that the agglutination of DHA-sensitized cells was not inhibited by the addition of HA. On the other hand, the sera resembled those from controls in that their agglutination of erythrocytes coated with HA could be completely abolished by HA."

On the basis of their original postulate, Cinader and Dubert thought they might

> ". . . expect an antibody response to DHA in *all* the rabbits having acquired tolerance to HA, and we would expect this to be very similar to DHA antibody absorbed *in vitro* by HA, that is, able to react with DHA but not with HA. An antibody of this kind could not agglutinate erythrocytes sensitized with HA in a way which could be inhibited by HA. In both these respects our results fail to confirm expectation. . . ."

They conclude that it seems

> ". . . more probable that acquired tolerance is due to some functional modification of the antibody-forming mechanism, a modification which may not require the continued presence of antigen."

Cinader *et al.* found that acquired tolerance to injected purified ribonuclease in rabbits did not affect the antibody response to unrelated antigens. They suggest that if the tolerance to a given antigen is due

> ". . . to the penetration of a locus in the immature cells by an intact antigen, it may be concluded that this locus either does not contain ribonucleic acid or that the continuous integrity of the ribonucleic acid in the locus is not essential for the synthesis of antibody."[16]

Cinader and his co-workers' acute analysis of their own results goes far to disprove their original postulate that antigen combines in the cell with antibody, and that the accumulation of this antibody inhibits further synthesis of antibody. It should be pointed out, however, that the conditions of their experiments were such that traces of antigen were probably continuously present, and as will be shown below, the presence of antigen in the cell might have effects other than those they visualize.

CONCLUSION REGARDING EXISTING THEORIES OF TOLERANCE

We may conclude from the above brief review that several of the existing theories of immunological tolerance are clearly incompatible with the known facts, and that none is completely satisfactory.

A "NUCLEATION" HYPOTHESIS OF IMMUNOLOGICAL IMMUNITY AND TOLERANCE

The hypothesis, proposed here, rests on a number of postulates, some of which are to be found also in other theories of antibody formation. The postulates, which are given below, should be regarded as being purely formal in the first instance, but in each case a possible interpretation in terms of cellular structure or function is given.

1. Antibody (Ab) is formed in the cell by a template, T, which is used up in the process. T may be visualized as being ribonucleoprotein which is used up in the formation of some few molecules of Ab. The theory thus far follows that of Schweet and Owen who present biochemical evidence that ". . . each template can synthesize a number of protein molecules before it becomes non-functional."[49]

2. T is formed (probably at a steady rate) in a non-specific form, N, which on contact with antigen (Ag) acquires a specific configuration, T, such that T produces Ab complementary to the particular Ag. The non-specific N may be formed in the nucleus and passed into the cytoplasm, but the exact site where it comes into contact with Ag does not affect the formal logic. There is evidence[18] that Ag may be demonstrated both in the nucleus and in the cytoplasm, so contact of Ag with N could occur in either place.

3. The template T is potentially self-replicating, provided that a critical threshold concentration of T is present. In other words, the theory is a "secondary template theory,"[58] similar in this respect to most current theories of antibody formation.[11] Evidence against the indefinite persistence of Ag in the Ab-forming mechanism (a necessary postulate of the so-called "primary template" theories) is given by Burnet and by Talmage. The possibility that ribonucleoprotein (known to be concerned with protein synthesis, and possibly the material counterpart of the postulated "T") may be produced in the cytoplasm, is now widely accepted[56] and will not be discussed further here.

The dependence of self-replication on a critical concentration, the phenomenon of *nucleation,* is perhaps a less familiar concept in the field of immunology (although it has been used in one theory of antibody formation by Jordon, quoted by Sevag[50]). However, critical values are well known in biology (all-or-none functioning of nerve and muscle, the necessity for a minimum of cells for growth to occur,[32] and the dependence of self-replication on a critical concentration can be formally compared with the phenomenon of autocatalysis in biochemistry[31]). The postulate is presented here without detailed biochemical interpretation, but in the belief that most biochemists would find it not unreasonable.

We may note in passing that the meaning of "self-replicating," or "auto-synthetic," has been analyzed by Hinshelwood[31] and Dean and Hinshelwood,[20] and it has been shown that individual cell components can follow the equations of an auto-synthetic process ". . . although not auto-synthetic in their own right. . . ."

The above "nucleation" concept is the crucial and most controversial postulate of the present theory, and the one from which the theory derives its name.

4. Ag comes into contact with N, and the antibody Ab produced by T is contained, in separate "spaces" (the "N-space" and the "Ab-space")

in the cell, such that the N-space is more readily accessible to and saturated by Ag coming from the blood than is the Ab space.

The existence of separate compartments or spaces in the cell is now well established.[46] One may visualize T (formed by contact of N with Ag) as being closely associated with an intracellular membrane separating two intracellular spaces, with Ab passing to the far side of the membrane as fast as it is formed. Alternatively, T might cross into the Ab-space as soon as it is formed from N, before it starts forming Ab. Both Ab and N might even be physically on the *same* side of a membrane, but by virtue of its intimate contact with the membrane, N might be in *effective* contact with Ag on the other side of the membrane, in the "N-space." Any of these situations would satisfy the formal condition.

It is known that in many protein-synthesizing cells, submicroscopic granules of ribonucleoprotein are aggregated along membranes of the endoplasmic reticulum; these membranes may be the barrier postulated between the Ab-space and the N-space. The tubules and cisternae of the endoplasmic reticulum are believed to communicate with the cell exterior in at least some cases,[46] and may well provide a pathway by which extrinsic particles could enter the cell without crossing any membrane. If the N-space in fact lies in the cisternae of the endoplasmic reticulum, it might be in more or less direct communication with the extracellular space, while if the Ab-space is in the ground cytoplasm of the cell, it would be separated from the exterior of the cell by the cell membrane, and/or the membranes of the endoplasmic reticulum.

5. Access of Ag to the Ab-space is easier in the embryo than in the adult. It has been shown that intact proteins penetrate foetal and neo-natal intestinal cells and not those of adults,[17,44] and it is reasonable to suppose that this differential permeability could apply also to those cells which are actually or potentially antibody-forming. It is here suggested that while Ag can enter the T-space readily in both adults and embryos, the barrier (the cell membrane?) between the Ab-space and the extracellular space is quantitatively more permeable in the embryo than in the adult.

6. Formation of Ab by T, and hence the associated using up of T, is dependent on the concentration of Ab in the Ab-space. Such a postulate is found also in the theories of Felton, and of Schweet and Owen, and is analogous to the "product inhibition" familiar in enzyme chemistry.

7. Ab and Ag coming into contact in the Ab-space interact chemically, and are then degraded without trace by the intracellular enzymes. This postulate is presented without detailed biochemical justification.

From the above postulates it is possible, by the assumption of suitable quantitative values, to envisage a dynamic scheme which fulfills most of the requirements of a theory of immunity and tolerance.

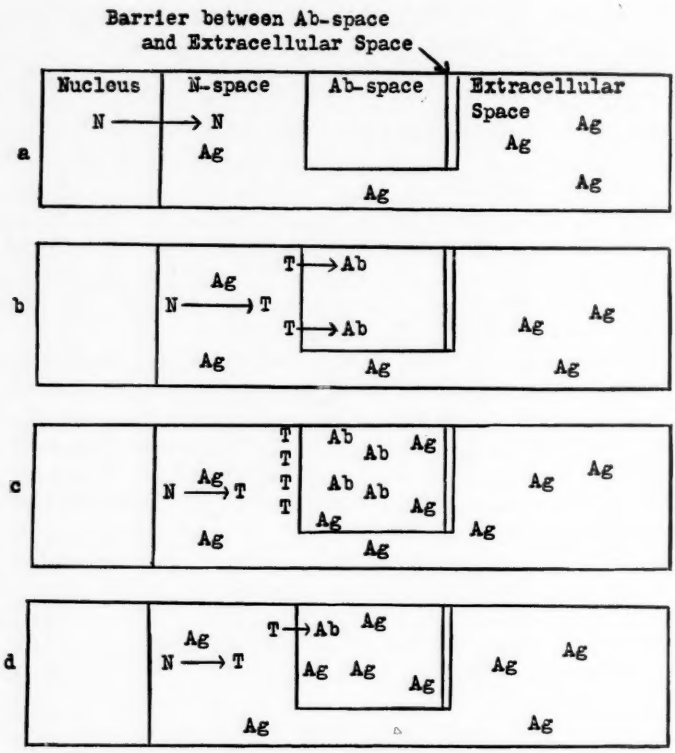

Fig. 1 (a). Formal diagram of the postulated "spaces" in the cell. Note that Ag from the blood can pass readily into the N-space, but must pass a barrier to enter the Ab-space. The non-specific N, formed in the cell nucleus, enters the N-space, where it comes into contact with Ag.

(b) In the presence of Ag, N gives rise to the specific template T. T gives rise to several molecules of Ab, which enter the Ab-space.

(c) For immunity to occur, Ab has to accumulate in the Ab-space. This it can do in the adult, because the access of Ag to the Ab-space is slowed down by the barrier. Once Ab starts accumulating, the formation of Ab by T is inhibited, and the using up of T is thus prevented. More T is continually being formed, and when the concentration of T reaches the critical level, self-replication of T commences.

(d) For tolerance to persist, all that is necessary is for any Ab formed by T to be immediately neutralized by combination with Ag in the Ab space. In the embryo easy access of Ag to the Ab-space is possible because of the slight resistance of the blood/Ab-space barrier: in the adult saturation of the Ab-space with Ag is still possible, despite the increased resistance of the barrier (see text).

TOLERANCE

In the embryo, autologous or foreign Ag from the blood will enter the Ab space readily and saturate it (postulate 5). Simultaneously, Ag will enter the N-space and induce the formation of specific T from the non-

specific N continually being produced (postulate 2) (Fig. 1). Specific Ab will accordingly be formed (postulate 1) and will pass into the Ab-space (postulate 4), where it will immediately be neutralized by combination with the excess of complementary Ag present (postulate 7). The specific T will become used up in forming Ab (postulate 1), and will therefore not accumulate to reach the critical level necessary for self-replication (postulate 3).

Let us assume some arbitrary values for the rates involved (Fig. 1): say that 5 molecules of N are formed in unit time, and that each molecule of T forms 5 molecules of Ab before becoming inactive. Let the volume of the Ab-space be one unit of volume, and let the concentration of Ag in the blood and intercellular space be 1000 molecules/unit of volume. In the embryo, then, there will be almost 1000 molecules of Ag in the Ab-space at any given moment, and (assuming that one molecule of Ag neutralizes one molecule of Ab) 25 molecules of Ag must enter the Ab-space in unit time for equilibrium to be maintained (because 25 molecules of Ab are formed in that period).

When the antibody-forming cells mature, access of Ag from the blood to the Ab-space will become more difficult (postulate 5), but for a high equilibrium concentration of Ag in the Ab-space to be maintained, only 25 molecules of Ag need cross the blood/Ab-space barrier in unit time. We must suppose that the concentration gradient, and the permeability of the barrier, will be such as to permit this.

Note that as long as Ag is still circulating in the blood, and hence able to enter the N-space and induce the formation of specific T, Ag in the Ab-space will continually be used up in neutralizing the Ab formed. Thus to maintain the concentration of Ag in the Ab-space which is necessary for continued tolerance, a continuous supply of Ag is necessary. On the other hand, if the level of Ag in the blood drops altogether, some Ag may persist in the Ab-space for a considerable time, since it is no longer used up in neutralizing Ab, which is no longer being formed. This explains the long duration of immunological tolerance after relatively small doses of non-living antigen.

Despite the blood/Ab-space barrier, the level of Ag in the Ab-space may rise rapidly even in the adult, provided an *overwhelmingly large* dose of Ag is given. Under these circumstances, the concentration of Ag from blood to Ab-space will be sufficient to overcome the barrier, and the conditions for tolerance will be met.

IMMUNITY

In the adult, the injection of a moderate amount of foreign Ag may cause the blood level of the Ag to rise to (say) 1000 molecules per unit of volume (note that this is the same concentration as that of the tolerated autologous antigen discussed above). Ag will enter the N-space, and induce the formation of T from N. Using the same arbitrary figures as above, 25 mole-

cules of specific Ag will be formed in unit time, and enter the Ab-space.

Simultaneously, a certain amount of Ag will pass the blood/Ab-space barrier, and enter the Ab-space. As there is initially no Ag in the Ab-space, the concentration gradient from blood to Ab-space will be higher than that postulated above for a tolerated antigen, so that more Ag will pass the barrier in unit time than postulated above—say, 60 molecules. While these 60 molecules of Ag would be ample to neutralize the 25 molecules of Ab, *if given enough time,* the rate of reaction of Ag with Ab depends on the *product of their concentrations* (law of mass action). If 25 molecules of Ab are neutralized in unit time in the presence of almost 1000 molecules of Ag, only 1 to 2 molecules will be neutralized in the same time in the presence of only 60 molecules of Ag. Accordingly, some Ab will *temporarily* accumulate. However, more N is constantly being formed at the usual steady rate, and is being modified to the T form by contact with Ag in the N-space. Some of this newly-formed T will *not* form Ab, being inhibited by the Ab already present in the Ab-space (postulate 6). Molecules of T not forming Ab, do not become inactivated. Therefore T will start to accumulate, and after a time the concentration of T will reach the critical nucleation level necessary for self-replication to commence (postulate 3). Large quantities of Ab will now be formed, and will enter the Ab-space, clearing it of Ag. The condition of immunity has now been achieved. Note that continued presence of Ag is not necessary for continued immunity, since T is now formed by self-replication and no longer depends on conversion of N by contact with Ag.

The difference between the primary and secondary immune response may perhaps be explained by assuming that in the absence of further quantities of Ag, the accumulation of Ab in the Ab-space would eventually completely inhibit further formation of Ab by T. Later contact of the cell with Ag (the secondary stimulus) might then somehow facilitate the release of Ab from the cell, and synthesis of Ab could then be resumed. This explanation of the secondary response is similar to that of Schweet and Owen[45] and of Stavitsky[55] and admittedly implies an action of Ag on the cell not contained in the original postulates.

To summarize, the condition for *immunity* to develop is a low concentration of Ag in the Ab-space of the cell, together with a relatively high concentration of Ag in the T-space. This condition will be met on antigenic stimulation of the adult, because of the relative inaccessibility of the Ab-space to Ag. The condition for *tolerance* is a relatively high concentration of Ag in the Ab-space, compared with that in the T-space. This condition will be met in the embryo because of the postulated easy access of Ag to the Ab-space of the immature cell, and will be maintained later provided a continual moderate blood level of Ag is maintained. Immunological tolerance may be partial or complete, temporary or permanent, depending on the proportion of the organism's antibody-forming cells which are effectively inhibited by the intracellular presence of antigen.

From the above discussion, it will be seen that the nucleation theory of antibody formation accounts for:

1. The formation of Ab in response to ordinary antigens in the adult.
2. The absence of Ab formation against an organism's own antigens.
3. The phenomenon of specific acquired tolerance.
4. The necessity for the continued presence of antigen for tolerance to persist.
5. The occasional occurrence of partial or incomplete tolerance.
6. The "secondary response."

A number of other immunological phenomena are explained or interpreted below, on the basis of the nucleation theory.

COMPETITION OF ANTIGENS

It will be noted that in the above treatment of the intracellular fate of Ag, it was tacitly assumed that only one antigen was involved. We may, however, suppose that in fact *all potentially antigenic molecules reaching the cell, including autologous antigens and substances to which the animal had acquired tolerance, would be treated by the cell in exactly the same way.* Antigens present in the N-space would compete with each other for N; the amount of specific T formed from N after contact with any particular Ag, would be a function of the concentration and perhaps also of the chemical nature of that Ag. Tolerance of, or immunity to a particular Ag would not depend on the *absolute* quantities of T or Ab formed in unit time, so much as on the *relative* concentration of the Ag in the N-space and in the Ab-space.

Competition of antigens for N would account for the phenomenon[7] of an animal failing to respond to a weak antigen, if this is injected together with a stronger antigen (especially if the weaker antigen is present in smaller absolute amount).

The nucleation theory also immediately explains the fact[15,33] that autologous and foreign proteins are cleared from the blood stream at the same rate (during the period before antibody formation starts), because even autologous proteins would continually be used up in neutralizing the corresponding Ab in the Ab-space.

Different antigens might compete with others, not only for N in the N-space, but also to some extent for Ab in the Ab-space. It is known that acquired tolerance of antigens of a related strain or species is more readily induced than tolerance of a more distant antigen. This could be explained by supposing that antibody formed in response to the nearly related antigen might cross-react slightly with the organism's own antigens. There would then be some degree of synergism in the Ab-space between the organism's own antigens and the foreign antigen, in absorbing Ab formed in response to the latter. This would result in tolerance to the foreign antigen being more readily achieved than if no such cross-reactivity occurred.

It has been claimed[18] that a cell actively producing Ab only produces one particular Ab. If this is true (it has been denied by Cohn and Lennox—cited by Lederberg,[37]) it can readily be explained on the basis of the nucleation theory. One may suppose that once replication of a particular T has occurred in the cell, and the cell starts producing large quantities of the corresponding Ab, then the cell physiology is changed in such a way that a different Ag can no longer induce the formation of Ab. This might occur by a change in the accessibility of the N-space to Ag, or by an inhibition of production of N by the large quantities of ribonucleoprotein (T) now present in the cell.

ACTION OF ADJUVANTS

Adjuvants could enhance antibody formation in at least two ways.

First, they would prevent rapid release of antigen into the blood and lymph, and thus ensure a long-continued and mild antigenic stimulus. The prevention of a rapid rise of Ag in the blood would be important, because otherwise Ag might enter the Ab-space of potential antibody-forming cells rapidly enough to cause tolerance in many of them.

Secondly, the lengthy persistence of Ag in the tissue depot, in the presence of a variety of chemicals, might cause minor antigenic changes in some molecules of the antigen. Even if the original form of the antigen was present in the Ab-space of a given cell in sufficient amount to absorb completely all of the corresponding Ab formed, its affinity for Ab formed in response to the altered molecule might be inadequate to prevent accumulation of such Ab, and hence the development of immunity. The converse might happen in a cell containing quantities of the altered antigen in the Ab-space: immunity might develop in such a cell against the original antigen. In this way the effective antigenicity of the original antigen would be raised.

ORGAN-SPECIFIC ANTIGENS, AND THE INHIBITION OF SOMATIC MUTATIONS

According to Billingham et al, the cellular substances which act as isoantigens are present in all cells of the organism. As they recognize, no isoantigen concerned with transplantation immunity can be indispensable to the organism, since the presence of such an antigen cannot be recognized (by their experimental methods) unless at least one individual of the species does not possess it, and is hence able to develop a transplantation immunity against tissue emitting the antigen. Billingham et al conclude that isoantigens are ". . . variants of a class of substances which serve some unspecialized metabolic function in the cell."

Now the organ-specific antigens which are known to exist, have in several cases[38] been shown to be widely distributed in the animal kingdom, with little or no species specificity. If this is a general rule, the failure of organ-specific antigens to play a part in transplantation immunity might simply be due to the host animal having a "natural" tolerance to organ-specific

antigens which it shares with the donor, rather than to a failure of such antigens to enter the circulation.

If organ-specific antigens indeed normally circulate (some antigens such as lens protein, thyroid colloid and sperm probably do *not* normally reach the antibody-forming cells[60]) this might provide a homeostatic mechanism for the control of mutant strains of cells. *Alteration* or *acquisition* of antigenic properties would in general result in inhibition of the mutant strain of cells, due to the provocation of an antibody response resulting in "rejection" of the mutant cells in the same way as a homograft is rejected. This homeostasis would break down (1) if the modified antigen was very similar to the organ-specific antigen, (2) if a large number of cells mutated simultaneously, flooding the antibody-forming cells with antigen and thus preventing an antibody response, or (3) if the antigenic change was not alteration or acquisition, but a simple *loss* of antigenic properties.

In harmony with the last possibility, Green reviews evidence that malignant change ". . . is due to loss of factors conferring immunological identity on the cells of a tissue."[28]

FORMATION OF AUTO-ANTIBODIES

For tolerance to a given antigen to persist, continued presence of that antigen in the Ab-space of the antibody-forming cells is necessary. Breakdown of this condition could occur in at least three different ways:

1. If, due to some disease process, a particular organ ceased temporarily to emit an organ-specific antigen, after a time the concentration of the antigen in the Ab-space might drop sufficiently for immunity to develop on resumption of the antigenic stimulation.

2. Combination with an adjuvant might alter the specificity of a previously tolerated antigen sufficiently to enable antibody formed in response to the altered antigen to accumulate somewhat in the Ab-space without being immediately neutralized by combination with the normal antigen. Cross-reactivity of such antibody with the normal antigen might be insufficient to enable the normal antigen to keep the Ab-space clear of the antibody, but still be sufficient to enable a damaging antibody-antigen reaction to occur in the tissues.

3. A change in the permeability of the Ab-space might make access of Ag more difficult. The difference in reactivity between embryo and adult is ascribed on the nucleation theory to a quantitative difference in the permeability of the blood/Ab-space barrier. If the resistance of this barrier becomes excessive (as an exaggeration of the normal aging process), antigens might no longer be able to maintain saturation of the Ab-space, and immunity to those antigens could then develop. Not all antigens would necessarily penetrate the barrier with the same facility. Size of molecule, charge, etc., might be important, and one might anticipate that auto-antibodies would be formed in the first instance to those antigens which pass the barrier less readily in the normal individual.

HAPTENS

The action of haptens can be explained in two ways. Firstly, a specific alteration of N might only occur on contact with a molecule of a certain minimum size, so that combination of haptens with protein would be necessary for their antigenic determinants to be effective. Secondly, the small size of haptens not associated with proteins might enable them to enter the Ab-space so readily that no immunity could develop. Combination with protein would be necessary to prevent this.

The route of administration of an antigen may be important for the above reason. Oral feeding of certain antigens prevents guinea-pigs becoming sensitized by subsequent skin application,[14] perhaps because in these animals the oral route enables the small antigenic molecules to reach the antibody-forming cells without prior combination with protein.

IMPROVEMENT IN QUALITY OF ANTIBODY

According to the nucleation theory, once the concentration of T in the cell reaches a critical value, self-replication of T would ensure continued immunity even in the absence of further supplies of Ag. This self-replication is envisaged as being in general accurate, resulting in a constant quality of T and a constant quality of Ab.

As suggested above in the discussion on the "secondary response", accumulation of Ab in the Ab-space would eventually completely inhibit further formation of Ab by T, and a later contact of the cell with more Ag might somehow facilitate release of Ab from the Ab-space into the extracellular fluid. If this later contact of Ag with the cell is mediated by an antigen-antibody type of reaction, cells producing a superior type of Ab (i.e. an Ab with greater affinity for Ag) would enjoy a selective advantage over other antibody-producing cells in chemical competition for circulating antigen. Cells producing such a superior Ab would thus not be inhibited to the same extent as cells producing an inferior type.

In this way, accidental variations in quality of T could result in a gradual improvement in the quality of Ab produced in the organism.

INTERPRETATION OF THE RESULTS OF CINADER AND DUBERT

A summary of the relevant facts is given above.

According to the nucleation theory, in a rabbit rendered tolerant to human albumin (HA), HA molecules are present in the Ab-space of the antibody-forming cells, and neutralize any anti-HA antibody formed. On stimulation with diazotized human albumin (DHA), there will in such an animal be enough reaction of the HA with any anti-DHA Ab formed to keep the level of the anti-DHA Ab in the Ab-space low, *for a time*. Some Ab with reactivity only with the diazo group (and which would hence not be absorbed by HA in the Ab-space) would be formed, but relatively slowly. Before it could reach the necessary concentration in the Ab-space to cause accumulation of the corresponding T, and hence replication of T and per-

manent immunity, one may suppose that DHA would have had enough time to penetrate the Ab-space, and prevent accumulation of such Ab. Thus most such animals would not react to DHA.

In some animals, however, antibody with only a weak reactivity to HA and a stronger reactivity to DHA would accumulate in the Ab-space before the Ab-space level of DHA rises sufficiently to prevent it. Immunity to DHA would then result. The Ab formed might still have enough reactivity with HA to combine with it if the Ab is present in excess, so that the HA present in the Ab-space would also eventually be eliminated. Further stimulation with DHA could then result in the formation of Ab reacting more strongly with HA.

A careful study of the implications of the nucleation theory will show that most or all of the results of Cinader and Dubert can be explained on the basis of the theory.

INDUCTION OF ACQUIRED TOLERANCE IN ADULTS

According to the nucleation theory, immunological tolerance to a given Ag could be induced even in an adult if penetration of Ag into the Ab-space can be obtained before much antibody is formed. Such penetration could in theory be ensured in the following ways:

1. By overwhelming the blood/Ab-space barrier by excessive quantities of Ag. This factor may well play a part in "enhancement"[53,54] and "immune paralysis"[26] although there is some evidence that other factors may also play a part in these phenomena.[4,5,6,21,22]

2. By temporarily inhibiting the formation of antibody by the use of metabolic blocking agents. Thus it has recently been shown[48] that tolerance to human serum albumin can be induced in adult rabbits by the simultaneous administration of 6-mercaptopurine.

"RUNT DISEASE", "HOMOLOGOUS DISEASE", "SECONDARY DISEASE"

It is now well established[35,51,59] that lymphoid cells homografted to newborn or x-rayed animals frequently react immunologically against the host. On the basis of the nucleation theory, one may suppose that while the level of circulating host antigen is sufficient to *maintain* tolerance, it is insufficient to *induce* tolerance in adult cells not previously exposed to the antigen. Several ways of preventing the reaction of the grafted cells are suggested by the nucleation theory:

1. The graft cells should, if possible, be from the same inbred strain.[59] This is in general not feasible, especially in clinical work.

2. The graft cells should be immature immunologically, so that they may more readily acquire tolerance to the host. While possible experimentally in animals, this immaturity might greatly lessen clinical application, since such immature cells would probably be valueless in replacement therapy in adults.

3. Lyophilized *host* tissue re-injected into the host at the same time as

the homograft, should prevent antibody formation by the graft by flooding the Ab-space of the graft cells with host antigen. Once this initial tolerance (or "enhancement") is achieved, the normal circulating host antigen should be sufficient to maintain the state of tolerance in the usual way.

4. Temporary prevention of antibody formation by administration of drugs[48] at the time of the homograft, might enable the host antigens to penetrate the Ab-space of the grafted cells before significant formation of antibody has occurred.

SUMMARY

A new hypothesis is proposed, called the "nucleation" hypothesis. It rests on the following postulates, discussed in the text:

1. Antibody (Ab) is formed in the cell by a template, T, which is used up in the process.

2. T is formed (probably at a steady rate) in a non-specific form, N, which on contact with antigen (Ag) acquires a specific configuration, T, such that T produces Ab complementary to the particular Ag.

3. The template T is potentially self-replicating, provided that a critical threshold concentration of T is present.

4. Ag comes into contact with N, and the antibody Ab produced by T is contained, in separate "spaces" (the "N-space" and the "Ab-space") in the cell, such that the N-space is more readily accessible to and saturated by Ag coming from the blood than is the Ab-space.

5. Access of Ag to the Ab-space is easier in the embryo than in the adult.

6. Formation of Ab by T, and hence the associated using up of T, is dependent on the concentration of Ab in the Ab-space.

7. Ab and Ag coming into contact in the Ab-space interact chemically, and are then degraded without trace by the intracellular enzymes.

From the above postulates, a dynamic scheme is envisaged which explains the formation of antibody in response to ordinary antigens in the adult, the absence of antibody formation against an organism's own antigens, the phenomenon of specific acquired tolerance, and a number of other immunological and related phenomena.

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A NEW, LONG-ACTING ANTIHISTAMINE-SYMPATHOMIMETIC COMBINATION FOR THE MANAGEMENT OF NASAL CONGESTION

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A FREQUENT problem in the management of chronic allergies involving the upper respiratory tract is the patient's feeling of listlessness and apathy. This feeling is often superimposed on the allergic symptoms and is reinforced by the depressant action associated to a lesser or greater degree with many antihistaminic preparations. We became interested in a new anti-allergic preparation* which combines two antihistamines with a sympathomimetic drug, tanphetamin. The drug is prepared in a long acting form which assures prolonged absorption from the gastro-intestinal tract.

During the past several years, there has been a marked increase of interest in long-acting, oral therapeutic agents. The theoretical benefits to be derived from long-acting medication is not only extension of optimal therapeutic effect. Its benefit also lies in assuring better control over dosage with a consequent reduction of undesirable side effects. Several types of oral, sustained, release preparations have been devised to try to obtain these results. However, quantitative measurements of drug absorption from oral, sustained release preparations have been neglected or at least rarely published. This has raised questions and occasionally prompted criticisms relative to claims made for some of the sustained release preparations.

Radioactive tracer studies were conducted† with six human volunteers by using titrated phenylephrine to determine blood levels of the drug. Blood levels were obtained at various time intervals after oral administration of the usual dosage form, the hydrochloride salt of the drug, and a sustained release preparation containing the drug as a protocolloid tannate complex.** The results obtained from three subjects on each preparation show that: (a) with time the sustained release form provides a gradually rising, then plateau-shaped blood level curve. The hydrochloride salt rapidly yields a high peak concentration; (b) blood levels from the hydrochloride salt drop off comparatively sharply but the tannate complex provides relatively consistent levels through the twelfth hour; (c) there is less variation in individual blood levels among subjects on the sustained release tannate complex than among those administered the hydrochloride.

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*Nalertan® tablets, manufactured by Irwin, Neisler & Co., Decatur, Illinois.

†These studies were conducted under the direction of Robert L. Bogner, Ph.D., Nuclear Science and Engineering Corporation, Pittsburgh, Pa.

**Durabond® Principle.

In this study we were interested in the answers to three questions of special concern in the symptomatic treatment of hay fever. First, would small doses of the drug given produce relief of symptoms? Second, would the length of relief be satisfactory? And third, would there be associated side effects such as drowsiness or undesirable stimulation?

It was hoped that this study would also serve as an evaluation, not so much for the three established constituents, but for the efficacy of the Durabond principle of controlled release that Cavallito and Jewell[1] report.

In contrast to customary prolonged-action agents, the Durabond repository mechanism[2] is built into the molecular structure of each component, which are present as gallotannic acid salts. During passage through the gastrointestinal tract, ionic interchange releases the pharmacologic agents at a sustained rate and in therapeutic amounts, regardless of the pH of the environment.

RESULTS

A total of thirty patients were selected. Of this number, twenty were suffering from ragweed hay fever and were the primary target of therapy. These patients had a previous clinical history of coryza symptoms during the ragweed pollinization season. They all had positive skin tests to intradermal testing with 500 Protein Nitrogen Units of ragweed. The other cases in this study were diagnosed as sinusitis (three cases), upper respiratory infections (four cases), and nasal congestion with questionable allergy (three cases).

All the patients receiving this medication were adults. Previous symptomatic therapy in the hay fever cases consisted of various antihistamines. Concomitant treatment in the form of hyposensitization was given to nineteen of the twenty ragweed-sensitive patients.

The therapeutic effect of this drug was considered excellent if the patient experienced 80 to 90 per cent relief of symptoms; good if 70 to 80 per cent of symptoms were alleviated; fair if 50 per cent of the symptoms were relieved, and poor if there was no apparent change in symptoms after taking the drug. The results were considered excellent by the patient in eighteen instances and good in twelve instances. The physician's clinical evaluation and examination of the nasal mucous membranes called the results of treatment excellent in fifteen patients and good in fifteen patients. We were particularly interested in observing the effects of this tablet, which contained Pyrilamine tannate, 25 mg.; chloropheniramine tannate, 8 mg.; and tanphetamin (d-amphetamine tannate), 10 mg.; in the individuals suffering with seasonal coryza. The relief of nasal congestion and sneezing was reported as excellent by thirteen patients, and good by seven patients in the hay fever group. The patient's response and the doctor's evaluation seemed to correlate in all instances.

Duration of relief was as gratifying as the amount of relief obtained, since it averaged between seven and eight hours. In no instance was it less than six hours, and in several cases the effects lasted for as long as

twelve hours. Therefore, it was felt that the claim of prolonged action due to the Durabond principle used in this product was justified by the clinical reports obtained from the patients.

The dosage that produced a favorable response consisted of one tablet taken twice daily, morning and evening. Therapy was given for a minimum of four days and a maximum of two weeks.

No undesirable effects were reported by any of the thirty patients. Their acceptance of this medication was good without exception and there were no complaints of fatigue, drowsiness or over-stimulation.

SUMMARY

A new, long-acting antihistamine-sympathomimetic combination drug (Nalertan®) for the control of allergic conditions of the upper respiratory tract was tested on thirty patients. Its ability to give delayed action relief with small doses and without inducing drowsiness was evaluated.

The results, especially in hay fever patients, were gratifying. The response was uniformly good. In most instances one tablet twice daily decongested the nasal mucous membranes for eight hours.

There were no undesirable side-effects noted with use of this medication. The patients did not report any evidence of fatigue or over-stimulation while using the drug.

It is felt that this drug helps alleviate some of the listlessness and apathy associated with allergic conditions. In conjunction with hyposensitization, Nalertan® is considered to be a valuable adjunct in the symptomatic treatment of hay fever.

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SCIENTIFIC INVESTIGATION

"The experimentalist," I once wrote, "has observed a fact. A fact is always interesting. But just as a work of art acquires all its value only if it is properly placed and properly lighted, a fact acquires all its value only if it is properly interpreted. Hence the experimentalist attempts such an interpretation, that is, he makes a hypothesis. Such a hypothesis obviously has no objective value. In order to give it a value, the experimentalist thinks out an experiment, that is, he creates the conditions required for the observation of a new fact which must establish the value of the hypothesis. The new fact leads to a new hypothesis and thus from experiments to hypotheses and from hypotheses to experiments the physiologist progresses in the cognition of the mechanism of life."—MAURICE ARTHUS, *Philosophy of Scientific Investigation,* Baltimore: The Johns Hopkins Press, 1943.

NASAL ALLERGY IN CHILDHOOD

Observations in the South Florida Area

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NASAL ALLERGY is a generic term the implications of which are broad but ill-defined. Is nasal allergy a symptom, a syndrome, or an entity? Although there may be arguments to the contrary, there is ample evidence to support the view that nasal allergy constitutes a syndrome or symptom-complex. The various patterns of nasal allergic disorders which develop in pre-adult life, if uncontrolled, usually continue on as an adult problem.

Arbitrarily, nasal allergy may be divided into three main groups: (1) perennial allergic rhinitis (PAR), (2) intermittent allergic rhinitis (IAR), and (3) seasonal allergic rhinitis (SAR).

PERENNIAL ALLERGIC RHINITIS

Perennial allergic rhinitis is a nonseasonal nasal disorder the onset of which usually occurs in infancy or early childhood with the tendency to persist throughout life. The nasal mucous membranes in perennial allergic rhinitis vary in color from gray to grayish pink, swell when the process is active and recede when it is quiescent. Despite occasional remission of many of the characteristic symptoms, mechanical nasal blockage remains fairly constant at all times. The clinical appearance of the nasal mucosa probably is one of the more positive physical signs which aids in identifying perennial allergic rhinitis.

Although it is generally feared that nasal allergic disorders lead to more serious allergic problems like bronchial asthma, this is not the case with perennial allergic rhinitis as far as the climate of southeastern Florida is concerned. More typically, the disorder becomes chronic with all the unpleasant sequelae of snorting, sniffling, hawking, retching, and coughing. In the Florida area, some of these symptoms become intensified at night because of temperature variations. Engorgement of the inferior turbinates, producing nasal blockage, may often be accounted for by change of body posture which occurs when the child lies flat on his back.

The more discomforting symptoms of nasal allergy include episodes of rhinorrhea and sneezing. The patient usually complains of intense itching of the eyes and nasal tip. The "allergic salute," described and popularized by Bowen,[1] is frequently observed. Children distort their faces, twitch and resort to all sorts of peculiar facial mannerisms in an effort to overcome the discomfort of nasal blockage and itching.[2] Because of the nasal ob-

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struction which becomes more or less complete when the child is in the supine position, snoring is common at night. During the day, unless the nasal airway is freed, the child's mouth is constantly open, at least partially, and the expression is one of vacancy. In the infra-orbital areas which are

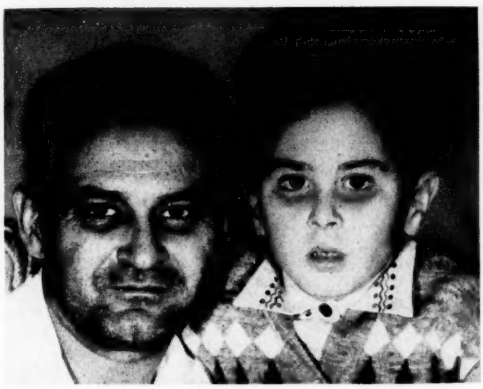

Fig. 1. Allergic eye shadows—"Allergic Shiners."

depressed, dark eye shadows can be seen in most children with perennial allergic rhinitis. For want of a better name, I have termed this feature "allergic shiners."[3] Often eye shadows are present in one or both parents (Fig. 1).

The symptoms of perennial allergic rhinitis may be intensified during periods of pollination mimicking or complicating seasonal allergic rhinitis. However, as the symptoms continue unabated throughout the winter, the true character of the disorder becomes apparent. There are exacerbations during heavy atmospheric mold concentrations; during cold, unseasonable weather changes; during attacks of acute upper respiratory tract infections; and during the so-called "house dust" season when heating appliances are used. The symptoms often are made more severe by exposure to environmental allergens of the inhalant variety, and by dietary indiscretions.[4]

INTERMITTENT ALLERGIC RHINITIS

I have termed the second variant of nasal allergy in childhood, *intermittent allergic rhinitis* (IAR). This name, I believe, is an appropriate one and aids considerably in clarifying the condition simulating, and in our experiences always followed by recurrent upper respiratory tract infections. Glaser[5] described the process as recurrent upper respiratory disorder (RURI), and in a survey[6] ranked it fourth in the incidence of allergic diseases in childhood. It was first described in 1931 by Cohen and Rudolph.[7] It differs from perennial allergic rhinitis (PAR) chiefly by recurrence and intermittent attacks of swelling of the nasal mucous membranes. These

attacks develop not only during respiratory tract infections but may occur also following exposure to various allergens inhaled or ingested. The infection is often a secondary event. The prolonged freedom from nasal congestion in quiescent periods is in decided contrast to the constancy of nasal blockage in perennial allergic rhinitis.

As a rule, intermittent allergic rhinitis progresses with each new insult to a full-blown infectious process with fever, nasal purulency, cough, and wheezing.

In intermittent allergic rhinitis (IAR), by the time the infant has attained the age of one year, he already has suffered from several episodes of acute upper respiratory tract infections. As the child gets older, the summer colds match those of the winter season. In the south Florida area, these summer colds do not necessarily indicate the presence of pollinosis or seasonal allergic rhinitis. Although usually the turbinal mucosa is glistening gray, it eventually may become bright red. The cytology of the nasal secretions changes from eosinophiles to neutrophiles.

If a chronic cough or wheezing ensues and remains unabated, then asthma is already present in 30 per cent to 50 per cent of the affected patients.[8] This feature differentiates intermittent allergic rhinitis prognostically from perennial allergic rhinitis, which, as previously stated, only occasionally develops into asthma in this Florida area.

In children, chronic hyperplastic alterations in the membranes of the maxillary and ethmoid sinuses may develop in perennial allergic rhinitis and in intermittent allergic rhinitis. In my opinion, the incidence of this complication is higher in the latter and probably hastens the onset of asthma. Blood eosinophilia seems to be conspicuous in these situations, especially if asthma also is present. Roentgen films of the paranasal sinuses are essential aids in the diagnosis and, therefore, should be a routine undertaking.

SEASONAL ALLERGIC RHINITIS

Hay fever, nasal pollinosis, and seasonal allergic rhinitis (SAR) are synonyms for the same disorder. Seasonal allergic rhinitis differs from perennial allergic rhinitis and intermittent allergic rhinitis by the recurrence of nasal symptoms during the pollinating season only. The constancy of the symptomologic pattern soon alerts the physician to the association of the nasal symptoms with the pollinosis.

Intense itching is experienced in the nose, eyes, palate and pharynx. Explosive paroxysms of sneezing, periorbital erythema from itching and upper lip edema from nasal discharge are common symptoms. Children are less tolerant than adults and appear toxic from the effects of the pollen, especially if pollination is heavy at the time.

In the southeastern Florida area, seasonal allergic rhinitis in childhood manifests itself in mild form, but when it does, the intervals are unpredictable and of short duration. This is in decided contrast to the explosive symptoms and protracted course so commonly experienced by children with

hay fever in the North. Furthermore, pollen asthma as an accompaniment of seasonal allergic rhinitis in childhood is practically non-existent in this Florida area. Recently, in Dade County, there have been reports of an increasing incidence of pollinosis in adults occurring from May to November. I have not, however, encountered a similar situation with children.

DIFFERENTIAL DIAGNOSIS

Allergic rhinitis is not actually an inflammatory process as the term *rhinitis* implies, but it is in a sense a rhinopathy. An allergy of long standing eventually becomes associated with an inflammatory process because of tissue changes provoked by constant irritating factors. The question whether the allergy precedes the inflammatory tissue changes, or vice versa, remains controversial.

Clinical tests alone do not always differentiate allergic rhinitis from other nasal disorders. Infective types of rhinitis simulate allergic rhinitis, but fever, sort throat and the history of exposure suggest that allergy as a factor can be disregarded. In some instances, however, an infective rhinitis may co-exist with an allergic rhinitis, confusing the picture until laboratory tests distinguish one from the other. The history, physical examination, cytology of the nasal secretions and the performance of carefully chosen skin tests will lead to a correct diagnosis.

There are several other diseases from which perennial allergic rhinitis must be distinguished, *vis.*, recurring adenoiditis, chronic sinusitis, and some nasal states attributed to congenital malformations and foreign bodies. If nasal allergy persists over a long period of time, it may lead to polypoid rhinitis or sinusitis. It should be noted, however, that polypoid rhinitis is of rare incidence in childhood. The pre-asthmatic cough of intermittent allergic rhinitis and perennial allergic rhinitis must be differentiated at times from pertussis and Kartagener's syndrome.

Although perennial allergic rhinitis in childhood may be considered a form of vasomotor rhinitis, the latter term is seldom used for children. Huber and Harsh[9] estimated a nonallergic etiology in approximately 30 per cent of their adult patients with vasomotor rhinitis. In pediatric practice, nonallergic causes of this disorder are relatively few, in my own experience, almost negligible.

The likelihood of the development of allergy to bacteria and their products must be recognized. Physical stimuli, such as the sudden onset of cold weather, may lead to pronounced nasal congestion; but whether these factors act in a nonspecific manner, or secondarily trigger an underlying allergic process, is unknown.

SKIN TESTING

The question of performing skin tests in early infancy for the purpose of clarifying the diagnosis has been answered by Peshkin.[10] He contended that there exists no contraindication to such procedure. Since, however,

food tests may be unreliable, dietary changes must rest on the physician's judgment, and often resort must be had to the trial and error method. In many instances, intradermal tests with inhalants suggest the therapeutic approach.

In children with seasonal allergic rhinitis, skin testing will usually reveal the offending pollens. As one approaches the winter season, one has to consider also intercurrent causes like molds or house dust, especially if positive skin tests are obtained with these agents. The symptomatology may then point to the development of perennial allergic rhinitis. The physical state of the child, his habits and environment play a prominent role in the rendering of a conclusive diagnosis.

THERAPEUTIC APPROACH

The syndrome of intermittent allergic rhinitis in infants and children, who suffer also from recurrent upper respiratory tract infections, responds favorably to treatment indicated by the history and scratch and intradermal testing. Many of these children already afflicted with pre-asthmatic cough and asthmatic bronchitis experience improvement after the administration of well-known inhalant extracts, vaccines, and bacterial filtrates (stock and autogenous), and the utilization of environmental and dietary control.

It is difficult to assess the true therapeutic value of immune globulin in the more resistant forms of IAR. Clinically, however, it appears to be helpful when used in large dosage (0.2 cc per pound body weight to a maximum of 10 cc) biweekly or monthly throughout the winter months.

The recommendation of Brown,[11,12] and of Loveless,[13] that in areas where pollinosis represents a serious problem a single annual dose of emulsified pollen extract should be given, merits consideration. In southeastern Florida, only small amounts of pollen are present in the atmosphere at irregular intervals. Rarely does one observe the explosive symptoms in children so common seasonally in the North. Furthermore, children migrating here from the North with symptoms of pollinosis improve remarkably in this climate.[14]

South Florida may never present too serious a pollinosis problem because of the persistence of a perennial growing ground cover. The latter tends to crowd out the troublesome, air-borne, pollen-producing plants. Pollen counts of ragweed, Bermuda, and Johnson grass are low. Some of our trees are prolific pollinators but produce very little trouble from a sensitization standpoint.

Exacerbations of low-grade pollinosis may result at times from ragweed and grasses growing on recently cleared land. This is only temporary and lasts until the ground cover takes over.

In treatment, one must recognize that often insects play a major causative role in respiratory tract allergy.[15] Feinberg[16] held that many instances of inhalant allergy in tropical and subtropical areas can be accounted for by the gigantic insect population. The insects ultimately break down and pollute the atmosphere with insect dust.

ANTIHISTAMINES AND CORTICOSTEROIDS

The child with nasal allergy treated solely with antihistamine preparations eventually will develop an intolerance to them. Continuous use of corticosteroids with or without antihistaminics may be dangerous. Apart from the development of well-known hazardous complications, which is inevitable if this sort of medication is utilized indefinitely, tolerance to a fixed dose may occur. As a consequence, increments eventually lead to still other complications and unpleasant side effects.

Judicious use of both antihistaminic and corticosteroid drugs has a place only in the short-term management of childhood nasal allergy. Although these remedies are known not to be curative, under some circumstances palliative effects are gratifying to the patient.

The use of nose drops for the relief of nasal stuffiness in my practice has been largely discontinued in favor of the newer oral nasal decongestant drugs. A preparation which has provided me with favorable results is a combination of chlorprophenpyridamine maleate, phenindamine tartrate and phenylpropanolamine hydrochloride (Nolamine®).*

Often overlooked in therapy are certain situations which retard favorable progress with conventional methods. For example, occasionally the obese child does not respond favorably to immunization therapy. Other children, though not obese, may present symptoms of chronic fatigue, listlessness, dry hair, dry skin and other borderline non-myxedematous symptoms of hypothyroidism. Because the condition does not represent a definite typical state of hypothyroidism, Hollender[17] has applied to it the term *hypometabolism.* In allergic rhinitis, the response to allergic management often is enhanced by treatment of this state with small doses of thyroid extract.

COMMENT AND CONCLUSIONS

Nasal allergy is a generic term whose implications are not clearly defined. The term, *intermittent allergic rhinitis,* should help clarify the classification of the rhinitides. Although the therapeutic response in perennial allergic rhinitis has not been too favorable, there is some satisfaction in that this form of rhinitis rarely eventuates in asthma.

Here in Florida, if children suffer from seasonal allergic rhinitis due to pollen, the condition is of short duration and, therefore, can be managed satisfactorily with modern drugs. Some children require no treatment at all. If, however, it is found that pollen is a contributing factor to the nasal disorder, it can be included in the treatment mixture.

Sole dependence on therapy with antihistaminics and corticosteroids is highly objectionable, and for curative purposes lacks the essence of a scientific approach. Such therapy is justified, however, for palliative effects, or for a short-term plan, but only if circumstances warrant.

The recognition that insect dust is a cause of rhinitis in tropical and

*Nolamine is a product of G. W. Carnrick Company, Newark, N. J.

subtropical areas has added to our knowledge of dealing more satisfactorily with some hitherto insoluble situations.

In the final analysis, the intercurrent problems of childhood must be seriously considered in deciding on the appropriate program of allergy management.

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THE INDUSTRY OF DISCOVERY AND OUTPUT OF KNOWLEDGE

"This peculiarity of research is a result of the fact that its output is knowledge. One may think of knowledge as consisting of a body of tested propositions. When two things are known, there is a possibility of seeing significant relationships between them which will yield practical applications. The larger the number of tested propositions, the more numerous are the cases in which the addition of a new tested proposition to old propositions will yield new useful applications and, in addition, will suggest hypotheses useful in adding still more tested propositions to the body of knowledge. Thus, the greater the body of existing knowledge, the greater is likely to be the value of the new discoveries."—SUMNER H. SLICHTER, "The Industry of Discovery," *Science,* 128:1610-1611 (Dec. 26) 1958.

HEADACHE AND ALLERGY

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HEADACHE and the common cold represent the most common of all human complaints.[10] Pain in the frontal area constitutes the most frequent form of headache. In this article, the recurrent headache of functional origin alone is considered. Excluded is the headache that is present in a wide variety of diseases associated with structural change in the skull or cortex. All the organic causes of headache account for a small per cent of chronic recurrent headche.[17] The functional headache is encountered most frequently as vascular disturbances, 90 per cent according to Wolff.[32] Classically, the vascular headache involves the frontal region, the forehead, although the eye, the cheek, and the upper teeth may also be involved.[10] Migraine, histaminic, cephalalgia, and tension headache are other varieties of functional headache. It is the author's opinion that the functional recurrent headache is predominantly of allergic origin.

Hansel and Helsinger[11] are of the opinion that migraine, the most severe type of the recurrent headache, is not found in more than 2 to 3 per cent of the population. Vaughan,[29] in making a study of the incidence of allergic headache in the cross section of a typical village, found that of all the allergic syndromes, migraine headache ranked fifth in allergic manifestations, behind hay fever, urticaria, gastro-intestinal allergy, and asthma, but ahead of vasomotor rhinitis, eczema, and angioneurotic edema.

As in other cyclic conditions, the preponderant opinion of the workers in this field is that the etiology is either psychological or idiopathic.[6,7,8,30,31,32] "Allergy may play a role in a small number of cases" is the usual grudging and hedging concession. What can be the reason for this apparent lack of association between allergy and headache?

1. The results of the past in the management of headache have been poor, even though every investigator does admit that there are instances of unquestionable connection with allergy, food or inhalant, in some cases of headache.[13]

2. The specific diagnosis of food allergy must be done methodically, and with the allergic point of view, as will be outlined later. This is time-consuming.[5] The nature of food allergy has not been completely understood by many, and therefore poorly investigated.[11] Rinkel and Randolph aptly expressed the situation when they said, "there has been difficulty on the part of both physicians and patients to place existing knowledge into actual

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practice. As in the past, the ease to disbelieve a new concept frequently overcomes scientific curiosity and its attendant desire to explore a new field. The dynamic field of food allergy has been completely misinterpreted or ignored by most physicians."[23]

3. There has been an unjustified faith placed in the value of skin test procedures for the recognition of food sensitization.[3,5,23,24,25,26]

4. Another great obstacle has been the persistence of associating headaches in terms of classification,[24] "rather than in terms of their etiologic basis."

5. The great majority of cases of headache are seen and treated by other physicians than allergists.[16] Their method of approach is usually combined caffein and ergot medication[2,15,18] with or without psychotherapy[4,7,19,30] and with few other measures.[3,20]

This author, in a study of recurrent functional headache extending over fifteen years, had a series of 212 cases with a satisfactory follow-up and analysis. Allergy was found by him to be the predominant factor in 82 per cent. His approach in studying these cases included (1) a history emphasizing the allergic point of view, (2) skin testing, (3) elimination diet studies, (4) the individual food ingestion test,[23] and (5) the use of continuing food diaries.

A complete history was first taken with particular emphasis on the allergic angle.[1] When an inhalant allergen proves to be the etiologic factor, it is most frequently not associated with a food allergen.[9] This is illustrated in the second case study described below. The history here is almost diagnostic, and usually confirmed by positive skin tests.[11] The importance of inhalants should not be passed over lightly; the author found that in thirty-seven of his cases (12 per cent) headache was caused by inhalants. Furthermore, the presence of specific inhalants, and odors in the environment should be checked into and noted. Randolph has demonstrated that headache and other manifestations often develop as a result of petro-chemical hypersensitization, from gasoline fumes to even the slight amount of gas escaping from the kitchen range.[22]

Of the author's 198 patients with food-induced allergic headache, 175 (88 per cent) were also affected with other allergic syndromes, such as hives, gastro-intestinal cramps, diarrhea, vomiting, asthma and others,[13] Some of these patients were sensitive to inhalants besides foods. In some women, the premenstrual period is the only time that they exhibit clinical allergy to food.[25]

Skin testing should be done, even though its fallibility is great,[25] because not infrequently valuable information is uncovered, which may point directly to the offending allergen, especially an inhalant.

The use of the elimination diet-studies as carefully worked out by Rowe[25,26] offers an excellent and probably the most important approach to bringing to light the offending allergenic foods. Rowe's so-called cereal-

free diet is the one of choice. Although the diet is termed by him "cereal-free," milk, cheese, egg, fish, fresh fruits, chocolate, nuts and spices of all kinds are removed in addition to cereals. In the author's studies, there were very few foods that proved etiologically significant that were not eliminated by this diet. Once the symptoms are controlled, omitted foods may be reintroduced; at first, one a week, and later, one every three days, simultaneously keeping a lookout for any recurrence of headaches.

The Rinkel-Randolph individual feeding tests[23] offer a provocative approach to discovering allergenic foods. The suspected food is taken out of the diet for four days and then reintroduced to the patient in its pure form. Deliberate test feedings should be done for the second meal of the day, and the patient should be observed for at least one-half hour before feeding and an hour and one-half following the feeding. Should there be no reactions with the initial feeding, it is wise to give next approximately one-fourth of the original amount of food, and continue observations for thirty minutes following this second feeding. In three to four days, a similar test to another food is given. This method of food study lends itself well in confirming the other methods. This provocative individual food feeding and testing method with some modifications was used by the Ungers in their study of "Migraine."[28]

Food diaries that are kept with all attendant reactions and with the time of occurrence form invaluable follow-ups for tracking down offending foods that have often been included in the diet without the knowledge of the patient. This method also serves to impress upon the patient that practically all attacks can be explained etiologically, that interdicted foods crept in through oversight, or that the patient failed to stay away completely from the offending foods. In the Rinkel-Randolph food tests, it is shown that the patient is likely to have an immediate sharp reaction after ingesting food to which he is highly sensitive and which he had previously avoided for four days. Such a patient thus knows what has made him ill. The chronic cumulative use of a specific food to which one is highly sensitive may likely be associated with a different pattern of symptoms in relation to meals. Paradoxically, immediately after a meal, the effects tend to diminish and then disappear when successive quantities of the food are taken while one is still reacting to the food recently ingested. The cumulative use of such a food is either not followed by a reaction, or the subject reports that he feels better after the eating than before. Randolph calls this phenomenon "food addiction."[21] That is why such patients rarely know that they are sensitive to common foods of the diet. This type of food sensitivity is the most common type. The clinical picture of "food addiction" is dominated by the inevitable recurrence of delayed symptoms.

Then, there are the so-called "cumulative reactors,"[23] which refer to foods that do not cause symptoms unless they are eaten in three to seven meals in close succession. The patients are asymptomatic if the foods are taken once a day, every other day, or once every third day. It is important

to make the diagnosis of "cumulative reactions" because we can then increase the number of foods in the patient's diet by interval usage of the food with the cumulative type of sensitization.[23,24]

There are cases of "concomitant food sensitization."[23,24] This implies a reaction to a food in the presence of an inhalant, which does not occur when the food is ingested in the absence of the specific inhalant. There is often a concomitant reaction between foods and dust, although that between food and pollen is more commonly known. Certain foods need to be eliminated during the pollen seasons to which the patients have symptoms, but may be restored after the pollen is no longer in the air. However, there is no procedure so satisfactory as the specific and absolute elimination of the foods to which the patient is sensitive, until he gains tolerance When tolerance is obtained, it is necessary to give the patient instructions as to how often he may use the food without losing tolerance. He must also be taught where he will encounter the food.

It is obvious how important it is to know whether the patient has actually eliminated the sensitive foods. This is especially so when there has been no response to treatment. The food diary serves its greatest purpose here.

Important contributory or secondary factors which trigger attacks of headache are revealed by the history and food diaries. Thus a recurrent headache may be noted only at the time of the menstrual period, because of the heightening of the allergic tissue reactivity then.[25,27] Emotional tensions, nervousness, and excitement may activate secondarily, potential allergies in many patients. The allergic balance may also be upset by acute or chronic infections, overeating, indigestion, constipation, physical agents, such as changes in weather, humidity, wind, odors, smoke, et cetera. The symptoms of headache may be wrongly attributed to these secondary nonspecific causes, largely because the physician cannot discover the responsible allergen. Often neuroses are blamed for headaches, whereas it is just the reverse. The persistency and chronicity of the headache increase potential nervousness and disturbed emotional states.

COMMENT

The cyclic recurrence of symptoms is characteristic of allergy, especially foods, according to Rowe.[25] So-called refractoriness or desensitization develops after symptoms have existed for a few hours to several days. During the attack, the antibodies which have increasingly bound themselves to the cells of those tissues in which the major allergic reactivity resides, are exhausted and disappear. For days or weeks thereafter, the causative allergen may be eaten or inhaled without any symptoms. Gradually, the antibodies again accumulate in the shock tissue (brain or meninges)[25] and then symptoms may reappear slowly, or at times even suddenly. Thus the patient may ingest the allergenic food daily, or inhale the causal allergen continuously, but suffer headaches only once a week, once in two weeks, or even much less frequently. As mentioned previously, attacks may be triggered by secondary factors.

DIAGNOSIS

The diagnosis of the etiologic factors cannot be made in the chronic recurrent headache of functional origin until allergy has been investigated and ruled out by the following method or equivalent:

1. History from the allergic viewpoint
2. Skin testing
3. Elimination diet studies
4. Rinkel-Randolph provocative food tests
5. Food diaries

RESULTS OF THE AUTHOR'S STUDY WITH ILLUSTRATIVE CASES

As stated earlier in this paper, the above five allergic methods were employed by the author in his fifteen-year study of 212 cases of headache of various degrees of intensity. Forty-eight (24 per cent) of the cases were of the typical migraine variety. However, all varieties of these functional recurrent headaches, no matter whether classified as migraine, atypical migraine, or histaminic cephalalgia, tension headaches were found to react similarly from the etiologic point of view, although the end product, headache, varied in intensity with different patients and at times in the same patient. The offending allergens were found in 164 cases, resulting in controlling the headaches in the same number of cases (82 per cent). When these interdicted foods or inhalants were re-introduced, the headaches returned.

Still better results undoubtedly might have been obtained if complete control of the patients could have been exercised, such as by hospitalization, or by a method similar to the one used by Kempner at Duke University in his study of control of hypertension with rice diet.[14]

Probably the objection will be raised that psychotherapy may have played the major role in obtaining the good results. Psychotherapy is admittedly present in any patient-doctor relationship, especially when unusual interest is shown the patient. However, this must be considered minimal, when the reintroduction of the offending foods brought the recurrence of the headaches, and the food diary follow-up showed that most of the headaches that recurred could be explained as interdicted foods entering inadvertently into the patient's diet.

There is a need for a continuous running history and an evaluation of the cause-effect relationship. It is therefore important that patients be under observation for at least a year. In the author's series of cases, it was possible to follow 124 (58 per cent) cases for over a year, because most of these patients were treated for other allergic syndromes.

A finding of special significance was noted by the author during the eighth year of the present study, especially since it repeated itself persistently. Furthermore, on reviewing the older cases, the same results were obtained. In the past seven years, the successive new cases only confirmed the original finding. It seems that certain foods have an untoward prone-

ness toward producing a headache of the functional variety, when they are the antigens in the antigen (food)-antibody reaction. Of course, any food might be proved the etiologic offender in such a case, but this particular group of foods was so commonly found in the lists of offenders causing headaches, that the number reached the significance of a possible common denominator. The value of this finding is obvious. Thus these foods are now removed in the initial elimination diet given to the patient, in addition, of course, to using the findings obtained through the history and skin tests. These foods are now given in the order of their frequency as allergens, as well as according to the intensity or severity of headache produced. They are:

Coffee	Cocoa, usually in form of chocolate
Onion (raw)	All nuts and seeds
Egg	Spices and herbs of all types
Chicken	Legumes, such as pea, bean, lima bean, peanut
Orange	

When nasal symptoms are found associated with the headache, milk may be included in this list, but in the pure cases of headache, it does not belong with the common denominator group of foods. In the case of coffee, the allergen usually resides in the coffee bean and not with the caffein, which is one of the main ingredients in the caffein-ergot medicinals, as cafergone and cafergot. These are of great value in relieving migraine.[2] It also aids in understanding why coffee and the related cola drinks are easily overlooked as etiologic agents. Caffein, occasionally, also may prove to be an offender. In such cases, caffein preparations will not prove of benefit in migraine, or in other types of headache.

ILLUSTRATIVE SELECTIVE CASES

Case 1.—S.K., a man of forty, presented complaints of recurring headaches of severe intensity. At times they were right hemicrania, associated with vomiting and then drowsiness. These symptoms were present for seventeen years, and required more than twenty-four hours to subside completely. He suffered from other allergies in addition, allergic rhinitis, and had eczema in his childhood. Skin tests were negative. On elimination diet studies, chocolate, nuts and seeds of all varieties, raw onion, egg, and milk were incriminated. Confirmation was obtained by the Rinkel-Randolph method. The patient soon realized the necessity of avoiding the above foods as a preventive of severe headaches. A follow-up study of the patient over the years indicated that he suffered prompt recurrence of headaches whenever he indulged in some of the allergenic foods (which he was prone to do) during periods when he felt well for a few weeks. He had an unusual craving for raw onions and peanuts, which dated back to adolescence.

Case 2.—A boy of fourteen was seen at the Consultation Service of the Mount Sinai Hospital with complaints of severe frontal and occipital headaches which occurred several times a week. They were present for almost two years, and seemed to be getting more intense. He was thoroughly studied by the staff of the Consultation Service, including a psychiatrist. The results were negative. He was then referred to the author for an allergic work-up. The skin tests yielded a definite posi-

tive reaction to glue. Tests to all other substances used were negative. From interviews with the boy it was brought out that he spent a great deal of his spare time building toy airplanes, in which glue was freely used. Apparently, the inhalation of glue was the sole cause for his headaches. This case demonstrates the value of the routine use of skin tests in allergy and the importance of inhalant allergy alone in headache.

Case 3.—N. O., a woman of forty-two years, had suffered with headaches for twenty years or more. These were almost always present starting two days prior to the onset of her menses and lasted three days. She also incurred headaches during the month. They were less severe than the other type. Moreover there was a history of eczema of both ear lobes and neck for years. There was also a strong family background of allergy.

Skin tests were negative. Elimination diets showed that chocolate, pork, nuts, coffee, tea, caffein, cola drinks, legumes, egg, chicken, milk, beef, grape, and melon played the etiologic roles in the headaches, and eczema. The interesting feature in this case was that the patient was sensitive to both the coffee bean and the caffein content of the bean; when fed some of the pure alkaloid of caffein, she developed a headache several hours later. Naturally, she did not get relief from headache remedies that contained caffein.

Case 4.—F. H., a married woman of thirty years, had a strong family history of allergy. She had suffered from migraine for thirteen years and bronchial asthma for five years. The migraine attacks always began approximately about three days prior to the onset of her menstrual period and lasted three to four days. An attack incapacitated her for at least two days. She was sensitive by skin tests to ragweed and house dust. The elimination diet added milk, beef, chocolate, pork, coffee, egg, chicken, pea, bean, mustard, black pepper, and orange. Ingestion of these foods was found to trigger and aggravate her asthma just prior to her menstrual period. Hyposensitization to ragweed and dust relieved her asthma to a great extent, but her migraine required meticulous avoidance of the allergenic foods. She strayed from her diet often because of carelessness, although instructions were repeated verbally and in writing almost weekly. Her infractions were pointed out from her food diary.

The uncooperative patient is a factor that must be reckoned with by the physician who is striving for results. In this case, the patient was truthful and admitted her lapses, but often patients are not so truthful; they do not admit to any dietary indiscretions. This type of omission is a handicap that can be obviated only by the discharge of the patient who is repeatedly unreliable.

Our patient was finally prevailed upon to carry out completely her instructions for a period of two months. She was free of all her original complaints for that period of time. On the reintroduction of foods that were considered offenders, her sick headaches recurred.

Case 5.—Mrs. R. K., a housewife of thirty-three years, had headaches for the eight years proir to her first office visit. They occurred on an average of twice a week, and lasted about half a day each time. She had suffered from ragweed hay fever for twenty-five years, and was treated until five years ago with satisfactory results. There was a decided bilateral positive family history to allergy. She was first seen by the author as a patient in the children's allergy clinic of The Mount Sinai Hospital at the age of eight years. Skin tests at that time were positive to ragweed, mixed feathers, pyrethrum, cat hair, mustard and radish. She received hyposensitization therapy to ragweed at the clinic for nine years, with satisfactory results. For the last four years prior to her first office visit, she received psychiatric

therapy in the form of analysis for a compulsive neurosis. She was afraid of meeting and mingling with people and of leaving her home without her husband or other member of her immediate family. In addition to analysis as treatment, the psychiatrist prescribed tranquilizers for the patient. No other change was instituted in her mode of living or diet. Not only did she not experience any improvement, she actually felt that she was getting worse. The allergic study was carried out according to the methods outlined above. The skin tests yielded positive reactions to ragweed, timothy, mustard and radish. In addition, the elimination diets added milk, orange, grape, grapefruit, cherry, canteloupe, watermelon, cocoa, coffee, nuts, pea, bean, and peanut. Her food history revealed that she had indulged in these foods often, particularly coffee and cola drinks, which she imbibed several times a day. Upon the elimination of these foods from her diet, her headaches were totally relieved. What is more significant, however, her analytic treatments which had continued, were now beginning to give her improvement without support from tranquilizers. She received hyposensitization to pollen and dust.

This case demonstrates the great value of the thorough allergic work-up in all allergic syndromes, even when frank and deep neuroses co-exist. The neurosis, in the case of R.K., apparently became more amenable to psychiatric treatment after the proper allergic control was instituted. There is no reason why it should not prove of value in similar cases.

SUMMARY AND A PLEA

1. In a series of 212 cases of recurrent headache of functional origin that were followed for a minimum of six months, 82 per cent were relieved after the elimination of the causative foods and inhalants wherever possible, and by the use of hyposensitization to the pollens and house dust in the presence of positive skin tests.

2. The method of allergic investigation included: (a) a history obtained with the allergic viewpoint in mind, (b) skin testing, (c) elimination diet studies, (d) individual provocative food tests, and (e) a running food diary associated with concomitant symptoms.

3. A group of foods was found to form a common denominator in demonstrating an affinity for bringing on the allergic headache when these foods were allergenic, namely: chocolate, all nuts, seeds, spices, herbs, legumes, coffee, onion (raw), egg, chicken, orange and milk, particularly in cases with associated nasal involvement.

4. A plea is made to allergists to take the initiative and work in neurologic, medical and opthalmologic clinics with cases of functional headache. Preferably, every alternate new case of headache admitted to that clinic should be studied by the allergist, and the results should be compared and reported. Other medical men may then realize the great importance of the allergic study in controlling functional headache.

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ERRATUM

In the paper by L. Bagratuni entitled "A Comparative Study of Topical Steroids, Antihistamines and Pollen Vaccine in the Treatment of Hay Fever and Hay Asthma" which appeared in the August (1960) issue of ANNALS, a misspelled word appeared throughout: promezathine hydrochloride. This should have read: promethazine hydrochloride.

INCIDENCE OF SUBSEQUENT RAGWEED POLLINOSIS IN PATIENTS WITH PERENNIAL BRONCHIAL ASTHMA AND/OR PERENNIAL ALLERGIC RHINITIS

A Study of 100 Patients with Negative Skin Test Reactions to Ragweed Pollen at the Time of Starting Specific Injection Therapy

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IN 1958, Chambers and Glaser[1] reported on allergic individuals who did not suffer from ragweed pollinosis at the time of skin testing, but who gave positive reactions to ragweed pollen extract. Of these individuals, 50 per cent developed ragweed pollinosis within twenty years: 88 per cent of this allergic group developed the pollinosis in ten years; 64 per cent, in five years. Therefore, the authors concluded that the practice of giving injections of ragweed pollen extract to such individuals, provided that they are also receiving injections of other allergens (house dust, for example), is justified as a prophylactic measure in areas where ragweed pollinosis is prevalent. Because of these findings, we felt that a study of individuals suffering from perennial bronchial asthma and/or perennial allergic rhinitis, who did not have ragweed pollinosis at the time of the original testing and who reacted negatively on cutaneous testing to ragweed pollen extract, might be worth while. Such a study might also serve as a control to the report of Chambers and Glaser. If a significant number of such individuals ultimately developed ragweed pollinosis while under treatment, one would have to consider whether or not to treat these patients prophylactically with ragweed pollen extract.

METHOD AND MATERIALS

Cases for this study were selected serially on the basis of those private patients who suffered from perennial allergic rhinitis and/or perennial bronchial asthma, but showed no symptoms or ragweed pollinosis when they were first tested between March, 1938, and December, 1948. Because of the studies contemplated when this clinic was opened, all allergic patients have been tested cutaneously with ragweed pollen extract. Those patients from 1938 to 1948 who gave a negative scratch test to ragweed pollen extract in a 1/50 dilution, and a confirmatory negative intradermal test to ragweed pollen extract in a dilution of 1/100, were recorded. In August, 1959, a follow-up study was started. Patients of all ages were included. Of 321 such

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patients, 100 were successfully followed up, either by personal interviews, telephone or letter. These 100 constitute the group of whom this study was made. Forty-nine had perennial asthma alone, twenty-eight perennial allergic rhinitis alone, and twenty-three had both diseases when first seen. These cases are tabulated in Table I.

TABLE I. DISTRIBUTION OF DISEASES STUDIED

Perennial bronchial asthma	49
Perennial allergic rhinitis	28
Both	23
Total	100

It is believed that these two manifestations of allergy, perennial bronchial asthma and perennial allergic rhinitis, are essentially the same disease of the respiratory tree. In the former, the smooth muscle of the trachea and bronchi are the shock tissues; in the latter, the mucous membranes of the upper respiratory tract. The fact that these two diseases so often occur together is additional evidence that this opinion may be correct.

RESULTS AND DISCUSSION

Figure 1 indicates the number of patients in various age groups, (1) who were subsequently afflicted with ragweed pollinosis, (2) who continued to suffer from perennial bronchial asthma and/or perennial allergic rhinitis without subsequent ragweed pollinosis, and (3) who lost all symptoms of allergic disease. Seven (7 per cent) of the 100 patients developed ragweed pollinosis. No patient in the six to ten-year group developed ragweed pollinosis. The asthma of only one patient over forty was eventually complicated by ragweed pollinois. The preponderance who developed ragweed pollinosis lay in the sixteen to forty-year-old group. Of the seven patients mentioned above, one had recovered from bronchial asthma; two have continued to suffer from perennial allergic rhinitis; one continued to have bronchial asthma and developed tree and grass pollinosis; and three others persisted with bronchial asthma and developed ragweed, then grass pollinosis. One might also infer from Figure 1 that of the patients referred to the allergist because of perennial bronchial asthma and/or perennial allergic rhinitis, those under five years of age stand a better chance of losing their allergies in ten to twenty years than do older individuals.

Table I shows that twenty-eight patients suffered from perennial allergic rhinitis (age range, five years to fifty-six years). Of these, only two (about 7 per cent), ages thirty-four and forty-four years, at the time they started treatment, developed perennial bronchial asthma. However, MacKinney and Glaser[3] have studied 123 children ten years of age or less, who were first seen because of perennial allergic rhinitis. Of these, 27.7 per cent developed bronchial asthma in an average of two and one-half years. Hence, in contrast to evidence present in Table I, perennial allergic rhinitis in children is to be regarded as an important precursor of bronchial asthma. Sherman and Kessler[4] stated that between 30 per cent and 50 per cent of

children with allergic rhinitis later developed asthma. However, they apparently included seasonal allergic rhinitis and did not distinguish, as did MacKinney and Glaser, between perennial allergic rhinitis and the recurrent upper respiratory disorder. On the other hand, Marks,[5] who did

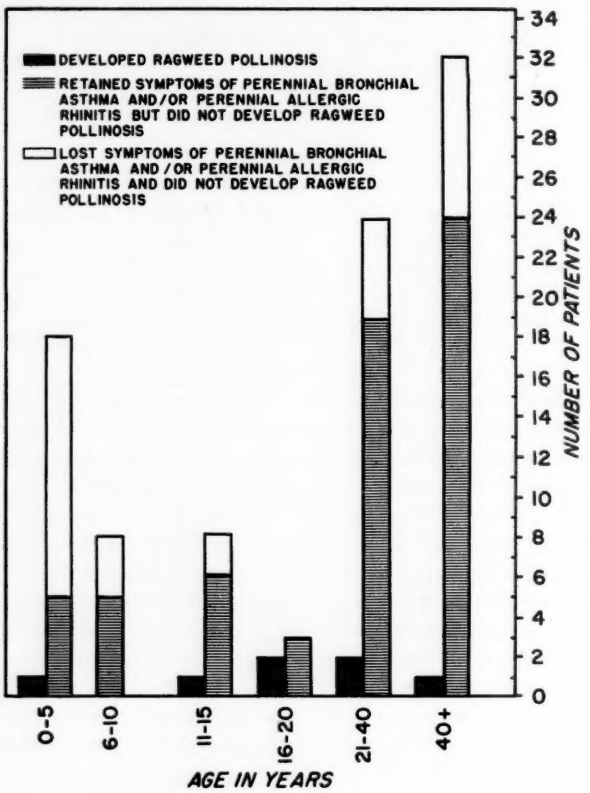

Fig. 1.

differentiate between perennial allergic rhinitis and the recurrent upper respiratory disorder (which he prefers to term intermittent allergic rhinopathy) noted that in his experiences with children, bronchial asthma rarely follows perennial allergic rhinitis. Perhaps this result may be due in part to the milder climate (southern Florida) in which he practices. Our study clearly indicates that perennial allergic rhinitis of adults is rarely followed by bronchial asthma.

Figure 1 also indicates that about 20 per cent of our patients were five years of age or less. This percentage cannot be taken as an index of the normal incidence of these diseases at various age groups because our practice is primarily pediatric allergy. Adults are seen on a consulting basis only.

This table, however, strongly suggests that the prognosis of allergic disease is much better in the very young age group, i.e., patients up to five years of age. The majority of patients (69 per cent) continued to have symptoms, and this percentage indicates the difficulties involved in the treatment of the two diseases studied. However, we did not attempt to determine the degree of improvement in the patients' symptoms. Experience indicates that in both of these diseases, almost all patients get a satisfactory measure of relief by combined allergic management, i.e., by environmental control, dietary therapy, symptomatic medication, specific injection therapy and psychosomatic support.

CONCLUSIONS AND SUMMARY

One hundred patients who suffered from perennial bronchial asthma and/or perennial allergic rhinitis, but did not have ragweed pollinosis when first seen and who reacted negatively on cutaneous testing with ragweed pollen, were followed for a period of ten to twenty years. The purpose of this study was to find out how many of these patients developed ragweed pollinosis.

Of these 100 patients, seven (7 per cent) developed ragweed pollinosis. This incidence is less than the incidence of ragweed pollinosis in this locality. For example, Glaser and associates[2] found that 13 per cent of high school children in Rochester, New York, suffered from ragweed pollinosis. If this study had been extended to older age groups, the percentage of the total population suffering from ragweed pollinosis would certainly have been significantly greater.

The above evidence indicates that prophylactic injections of ragweed pollen extract are not warranted in patients who suffer from perennial bronchial asthma and/or perennial allergic rhinitis, who have a negative cutaneous test to ragweed pollen, and who do not suffer from ragweed pollinosis.

When we consider this report in the light of the study of Chambers and Glaser,[1] the definite prognostic significance of a positive test to ragweed pollen in a person with an allergic disorder who does not suffer from ragweed pollinosis is evident.

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ANAPHYLACTOID ALLERGIC REACTIONS TO INFLUENZA AND POLIOMYELITIS VACCINES

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THE FREQUENT use of influenza vaccine, poliomyelitis vaccine, and other immunizing agents, lends importance to even the rare and unusual adverse reaction to their administration. Allergic reactions caused by these injectable agents run the gamut from severe local reactions,[1] severe delayed serum-sickness type reactions,[2] to immediate reactions which result in anaphylactic shock.[3,4] The practicing physician should be aware of the possibility of unexpected allergic reactions, despite the fact that they are rare.

Three instances of severe anaphylactoid reactions variously termed constitutional, systemic or shock reactions, form the basis of this report. Two reactions followed the injection of monovalent influenza vaccine, and one followed an injection of poliomyelitis vaccine. In the first instance, immunologic methods showed the reaction to be due to the presence of silk antigen in the biological substance used. No specific constituent could be identified as the provocative agent in the other two reactions reported here.

These three patients were referred to one of us (J.F.) to determine their suitability for future vaccine therapy or immunizations, because untoward reactions to a previous injection had been observed.

REACTIONS TO INFLUENZA VACCINE

Case 1.—L. G., a nine-year-old girl, was injected intracutaneously twice in one week intervals with 0.1 ml. of monovalent influenza vaccine (Company B), with no untoward reaction. Three weeks later, a third injection of 0.1 ml. of monovalent influenza vaccine (Company A) was given. Within ten minutes an urticarial lesion measuring 2 x 2 cm. and erythema developed at the site of the injection. Within another ten minutes, the patient complained of tightness of the chest and itching of the palms and scalp. Sneezing, rhinorrhea and coughing ensued. She soon appeared restless and apprehensive, developed a generalized flush, and complained of increasing tightness in the chest. The rectal temperature was 99.6° F., the pulse was 110, respirations were twenty per minute, and the blood pressure was 130/70. The lungs were clear on ausculation.

Tripelennamine Hydrochloride (Pyribenzamine® 50 mg.) and epinephrine suspension 1:200 (Sus-Phrine® 0.1 ml.) subcutaneously produced partial relief in twenty minutes. The flush subsided completely in two and a half hours.

The patient had mild perennial allergic rhinitis with exacerbations during the pollen season. On two occasions, she developed generalized erythema, pruritus and

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TABLE I. RESULTS OF PASSIVE TRANSFER TESTS ON SITES PREPARED WITH SERUM OF PATIENT L. G. (CASE I) AND WITH SERUM D. W. KNOWN TO CONTAIN REAGINS TO SILK

Antigen Tested	Pharmaceutical Company	Results on Sites Prepared With					
		Serum L. G.				Serum D. W.	
		Recipient 1		Recipient 2		Recipient 3	
		Test	Control	Test	Control	Test	Control
Vaccines:							
Influenza	A	+++	0	+++	0	+	0
Influenza	B	+	0	+	0		
Influenza	C	0	0			0	0
Silk .01 mg N/ml.		+++	0	+++	0	+++	0
Egg .01 mg N/ml.		0	0	0	0		
Penicillin G 5,000 units/ml.		0	0				

urticaria while wearing a silk dress which had to be discarded. There had been no reactions to previous immunizations to diphtheria, pertussis or tetanus. The patient's mother and father have hay fever.

Passive transfer tests with influenza vaccine (three brands), silk, egg and penicillin were performed, utilizing three recipients. Two recipients had been prepared with serum from Case 1 (L.G.) and, for purposes of comparison, one with serum of a patient (D.W.) known to be sensitive to silk. In all three, positive reactions were evoked to silk and to the influenza vaccine of Company A (Table I).

Case 2.—R. G., a six-month-old male child, at the age of four and a half months had been given an intragluteal injection of influenza vaccine (0.5 ml., brand could not be recalled by the referring physician). Five minutes later, his body became limp, and he lapsed into coma. An injection of aqueous epinephrine 1:1,000 was given, with slight improvement. Although he opened his eyes, they were still "rolled up." A second injection of epinephrine resulted in further recovery within an hour and a half. The child remained tired, drowsy and listless the rest of the day. Next morning, the eyelids were swollen with slit-like openings. He was irritable and cried considerably. Convalescence was complete by the third day.

At the age of eight months, this patient was seen again by one of the authors (J.F.) because his mother had noted clogging of the nose and wheezing in the morning and evening during the preceding three weeks. In addition, there was an eczematous rash on the neck and upper chest. These findings were consistent with a diagnosis of bronchial asthma, allergic rhinitis and contact dermatitis.

It is relevant to mention that egg had never been fed to the patient and that later, at the age of two years, hives reportedly developed after its first ingestion. Previously, the ingestion of all meats and poultry had produced hives. A convulsion was observed during an upper respiratory infection with 105° F. temperature. The mother has hay fever and asthma; the father has hay fever.

Passive transfer studies performed on two recipients revealed completely negative results to silk (.01 mg. N per ml.); egg (.001 mg. N per ml.); penicillin (500 u.); and monovalent influenza vaccine companies A, B, and C. Thus no information as to the etiology of his severe reaction to the influenza vaccine was obtained.

On subsequent visits, in an attempt to start immunization of the child, by now one year old, the following tests were performed:

Scratch tests to Triple Antigen (Diphtheria-Tetanus-Pertussis, Company D) 1:10 and full strength were negative.

One month later, direct intracutaneous tests with the same vaccine were also negative. However, the parents reported that on the way home the child was excessively

sleepy, with brief dozing episodes. At noon the following day, he fell asleep suddenly while eating. Several hours later, the parents noted a raised papule with erythema around the sites of the two tests. The child's eyelids and brows were slightly puffy. Two days following, examination showed that the small raised papules were still present. The significance of this episode is difficult to evaluate.

DISCUSSION

The immunologic studies by passive transfer in Case 1 suggest that silk provoked the anaphylactic response, inasmuch as there was a strong positive cutaneous reaction to silk and to the influenza vaccine of Company A. Correspondence from this manufacturer acknowledged that silk filters had been used in the manfuacture of their influenza vaccine, although this practice was being discontinued.

This finding was not unexpected. Recently, the presence of traces of silk as a contaminant in several biological injectants, resulting from filtration through this medium, has been reported as the cause of anaphylactic reactions following administration. Rosenblum[5] was the first to report on a patient with marked sensitivity to silk which was found to be present in the tetanus toxoid to which he had reacted. Shortly thereafter, Friedman and his associates[6] reported a severe allergic reaction in a silk-sensitive child, following an injection of typhoid-paratyphoid vaccine similarly contaminated with silk. Brown and Coleman[7] reported severe immediate allergic reactions following injections of combined antigen (diphtheria and tetanus toxoids, and pertussis vaccine), human gamma globulin, and tetanus toxoid, all of which had been passed through silk filters.

One of us (M.C.)[8] reported the presence of silk antigen in four out of five brands of poliomyelitis vaccine tested, as well as in other biological agents including toxoids (diphtheria and tetanus), toxins (diphtheria toxin used in Schick testing), antitoxin such as tetanus antitoxin, triple diphtheria-pertussis-tetanus antigens, typhoid vaccines, combined catarrhal vaccine, human gamma globulin, Vitamin B_{12} and crude liver extracts. He also tested 250 allergic patients intracutaneously to silk extract and found that 27 per cent developed positive reactions. While it is not possible to determine the number of clinical reactors to silk, it would appear that there are sufficient numbers in the population to make this a dangerous contaminant of injectable materials.

Unrecognized reactions to silk probably have occurred in the past. Allergic reactions to such presumably innocuous substances as gamma globulin[9] which have been reported in past years may have been due to this causation. Sensitivity to silk could also explain some of those unusual instances in which patients appear to be allergic to a wide variety of seemingly unrelated biologicals. Reactions to these vaccines were attributed to the biological itself and, as a result, many patients were deprived of further immunization.

It should be pointed out that silk filters have frequently been used in the preparation of many injectable substances. In fact, some companies even filter distilled, de-ionized water through such filters, and use this water as a

vaccine diluent. Stimulated by these reports, most manufacturers of biologicals have begun to discontinue the use of silk filters. There are many alternatives such as filters made of glass, paper pulp, asbestos, nylon and stainless steel. Where silk is used, it should be obligatory that the label and packaged instructions indicate its presence, and a warning included as to administration to silk-sensitive subjects.

Silk contains a relatively simple protein of the fibroin family, the members of which exhibit considerable insolubility in neutral aqueous solutions. The carrying solvent of the vaccines discussed here is a saline solution which on more than one occasion during the manufacturing process is brought into contact with a silk filter. The additional effect of pressure during the filtering process may increase the total fibroin dissolved by the mechanical action of shredding the silk strands. Even though certain thermodynamic considerations might suggest a slight decrease in solubility with increased pressure, this factor would be operative only during the actual filtering process; if any suspended particles of silk were then present some added fibroin would probably dissolve upon the relaxation of pressure.

Sensitization to silk may develop after cutaneous or inhalational exposure to materials made of silk, or after injection with agents contaminated with silk, or by cross-sensitization with other biologically related insects, as Feinberg has indicated.[10]

Atopic patients allergic to silk should be advised of the possible untoward effect of biological agents. They should, of course, be skin tested with the intended injectable material before its administration. Moreover, testing for sensitivity to silk should be routine in allergy practice.

In Case 2, where no etiologic factor could be identified, passive transfer tests were done on blood drawn several months after the anaphylactic episode. It is thus possible that the reagins spontaneously disappeared in the absence of amnestic re-exposure to the incitant.*

Alternatively, the acute phase of his reaction characterized by sudden loss of consciousness and muscular relaxation, might have been due to a stress mechanism or to accidental introduction of the vaccine into the vascular system. This syncopal episode may have been followed by an accelerated serum sickness syndrome, possibly due to the egg or meat anlages which are present in influenza vaccine.

REACTION TO POLIOMYELITIS VACCINE

Case 3.—R.A., an eighteen-year-old boy, received his first injection of poliomyelitis vaccine, 1 ml. (brand could not be recalled by the referring physician) in June, 1956. Within a few minutes, he sneezed violently and developed marked edema of the face, including the eyelids. Breathing became increasingly difficult and generalized hives extended over his entire body. He soon lapsed into coma and became pulseless.

*Studies to be published on children sensitive to egg by one of the authors (J.H.F.) revealed instances where specific reagins to egg disappeared from the skin and blood within a few months in the absence of further ingestion of egg.

The acute phase subsided with the subcutaneous administration of epinephrine. Adrenocorticotropic hormone was also given. Severe hives continued for the ensuing three days. On the second day following the injection, he had severe recurrent abdominal pain. On the third day, a temperature of 101° F. developed. By the fourth day, all symptoms cleared, although he complained of weakness for several days thereafter.

TABLE II. RESULTS OF PASSIVE TRANSFER TESTS ON SITES PREPARED WITH SERUM OF PATIENT R. A. (CASE III)

Antigen Tested	Pharmaceutical Company	Recipient 1		Recipient 2	
		Test	Control	Test	Control
Vaccines:					
Poliomyelitis	D	+++	0	++	0
Poliomyelitis	A	0	0	0	0
Poliomyelitis	E	0	0	0	0
Poliomyelitis	F	0	0	0	0
Poliomyelitis	G	0	0	0	0
Influenza	B	0	0	0	0
Silk .01 mg N/ml.		0	0	0	0
Penicillin G 5,000 units/ml.		0	0	0	0

In the past, the patient had received the following inoculations without reaction: penicillin on several occasions, the last injection five years prior; tetanus toxoid, basic series in 1939 and boosters in 1942, 1949, and 1953; typhoid injections, three in 1942; smallpox vaccination in 1947 with "immune take."

R.A. has hay fever (untreated) and dislikes egg, although he eats it occasionally.

The passive transfer studies with the serum of this patient (Table II) indicate that there is something as yet unidentified that is present in the poliomyelitis vaccine of Company D to which this patient is reactive. This agent is not silk or penicillin, which are present in the other four brands tested. The manufacturer suggests the possibility of a difference in the preservative used.

DISCUSSION

It was strange to most physicians with an immunologic orientation that no major reactions to poliomyelitis vaccine had been reported during the intensive program against this disease in which large segments of our population were inoculated. Nevertheless, many clinicians were aware of, or even had personal experience with, these severe reactions.

Poliomyelitis vaccine, according to government standards,[11] contains—

1. Medium 199 or modifications thereof. This is a kidney cell culture medium, containing vitamins and amino acids of small molecular size. Its allergenic potential is low.

2. Horse serum, the allergenic potentiality of which is high. However, final concentration in vaccine must be less than one part in one million.

3. Phenolsulfonphthalein, 0.002 per cent, a dye used as an indicator.

4. Formaldehyde, 1:4,000.

5. Preservatives: Methyl-and propyl-paraben, Wyeth; thimerosol (merthiolate) plus tetrasodium salt of ethylene diaminotetraacetic acid (versene),

Lilly; benzothonium (Phemerol) chloride, Parke Davis; or other preservative at the manufacturer's discretion.

6. Poliomyelitis virus protein and nucleoprotein.

7. Antibiotics: Penicillin, 200 units per ml., and streptomycin, 200 units, are present in the original culture medium. After dilution, washing, filtration and inactivation, the completed vaccine has from one to 30 units of penicillin per ml. Until 1956, the manufacturer had been required to reconstitute the vaccine to the original level by adding antibiotic. Since then, vaccines of most manufacturers contain from less than one unit to a maximum of 200 units of penicillin per ml. Wyeth Laboratories, however, have replaced the "destroyed" penicillin with polymyxin B. Thus the penicillin content of Wyeth's finished vaccine is reportedly below 0.0001 units per cubic centimeter.

A numerically limited study by Siegal on penicillin-sensitive subjects indicated lack of reactivity to poliomyelitis vaccine.[12] However, subsequent clinical experience has modified this concept of the nonantigenicity of the penicillin content of this vaccine.[13,14,15] It was illogical to expect that limiting the amount of penicillin to 200 units per ml. in poliomyelitis vaccine rendered it safe to exquisitely penicillin-sensitive subjects. There are reports which demonstrate reactivity to much smaller amounts.[16]

COMMENT

In addition to silk antigen as a contaminant of manufacture, and to such additives as penicillin or streptomycin purposely introduced as preservatives, there are other components in immunizing agents reputedly productive of severe allergic reactions. The residue from chick embryo, on which influenza, typhus and yellow fever vaccines are prepared, has produced anaphylactic shock in egg-sensitive individuals because of the antigenic relationship between the embryo and egg.[3,17]

Components of the bacterial culture medium, such as proteoses and peptones may also be antigenic. These have been incriminated in severe reactions to tetanus toxoid.[18]

Unidentified substances which enter the vaccine as degradation products may become allergens. This is suggested in Werne and Garrow's report.[19] They describe identical twins who died shortly after booster injections of diphtheria toxoid combined with pertussis vaccine.

Although no penicillin may be contained in the vaccine itself, penicillin may have contaminated syringes or sterilizers. This contamination has been shown to be of sufficient magnitude as to produce allergic shock in highly susceptible penicillin-allergic individuals.[20]

Horse serum derivatives whose antigenic potential has long been recognized, and which are contained in tetanus antitoxin and diphtheria antitoxin, are also found in gas gangrene and snake venom antitoxins. These derivatives are the most common cause of fatal or near fatal anaphylactic reactions to injections. As far as the writers are aware, anaphylactic reactions to the in-

trinsic organism of the vaccines based on a skin-sensitizing reaginic mechanism have never been shown.

It is well to remember that adenovirus vaccine is prepared like poliomyelitis vaccine, on monkey tissue culture. Reactions now seen with the poliomyelitis vaccine can be—and very likely will be—encountered with increasing usage of adenovirus vaccines.

CONCLUSIONS

1. In evaluation of the allergenicity of injectable biologicals, consideration must be given to the inadvertent introduction in the course of manufacture of potent antigenic substances.

2. The desirability of skin testing allergic individuals to biologicals prior to immunization is suggested. The procedure applies especially to patients known to be hypersensitive to silk or insect protein, penicillin, egg or chicken.

SUMMARY

Two instances of severe, immediate, allergic reactions to influenza and one to poliomyelitis vaccine are analyzed and immunologic studies presented.

In one instance, sensitivity was proven to silk which had been present as a contaminant of manufacture in the serum used. The potentially anaphylactogenic components of the vaccines given the other two are discussed.

ACKNOWLEDGMENT

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EXTRAPOLATION TO HUMAN SUBJECTS

We are on less scientific grounds when we use the experimental results to estimate the safe human intake. It is common practice to consider that the human population must receive in foods, no more than one-hundredth of the amount which has no effect upon experimental animals, on the grounds that humans may be ten times as sensitive as the animals, and that the weak human may be ten times as sensitive as the average human. If the utility of the substance is great, a factor less than 100 may be used; if the type of injury is particularly menacing and irreversible, a factor greater than 100 may be used. Since the factor is usually applied to the concentrations of the substance in the diet, there is actually a ratio greater than 100 between the experimental intake and the human intake judged safe, because effect depends upon molar concentrations, proportional to grams per kilo per day. No account is taken of the fact that small animals eat more than do humans. Nevertheless, I see no justification in quibbling over what the value actually should be, because it is at best an over-all guess having no relation to any one substance. It is convenient to use one standard for every substance, as long as we are unwilling or unable to determine the species ratio for each separate substance. Continued reliance on the factor of 100 gives increased confidence that it is large enough to prevent trouble, and not too large to hamper technology, although this has not been demonstrated. —Henry F. Smyth, Jr., Mellon Institute, Pittsburgh, Pennsylvania, from "Recognition of Toxicology as a Scientific Discipline," *Fed. Proc.*, 19:43 (Sept.), 1960.

PSYCHODYNAMICS OF THE ALLERGIC PATIENT

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EVER SINCE VON PIRQUET, it has been known that the allergic patient may have an abnormal antibody, the reagin. Because of the presence of the reagin, the affected person reacts to certain protein substances, the allergens. This reaction, in turn, causes him to produce histamine and similar substances and subsequently a variety of most distressing symptoms. But even in Von Pirquet's time, it became clear that this was not the entire explanation and that all allergic disorders were hardly as simple as proposed. It was noted, for example, that clinical allergy was not synonymous at all with immunologic allergy. An individual could show no demonstrable allergenic sensitivities and yet have symptoms identical with clinical allergy. The converse of the above situation also was described; namely, the presence of numerous sensitivities as demonstrated by skin tests in persons quite free from all allergic symptoms. Moreover, it was frequently remarked that massive relief of incapacitating symptoms could often be obtained by placebo medication. It was also noted that a simulated allergen could sometimes induce the allergic response, such as the famous example of Osler, who by proffering to the patient a paper rose, produced sneezing, lacrimation and nasal discharge in a person sensitive to roses. It was further described that the precipitating factor, the allergen, if we may call it this, need not be a substance at all, but could be a symbol or a person, and that a patient might react with typical allergic symptoms to a person, a situation, or a frustration. The very term allergy became common parlance in lay speech, and with as much insight as with humor, jokes were made about mother-in-law allergy.

This panorama of allergic disorders presents to physicians a special challenge. All of these data clamor for explanation and should challenge everyone in the field of medicine to formulate hypotheses broad enough to be generally applicable to these many paradoxical instances. It is for this reason that the specialty of allergy occupies a special and enviable position among medical specialties. Here is the opportunity to do work on the threshold of medical knowledge, for its subject matter spans (more broadly than does any other field of medicine) that dim and indefinite borderland between the strictly physical and the strictly psychic illnesses. It is a field rich with opportunity for broadening the knowledge of essential life processes.

The specialty of psychiatry, too, by the nature of its subject matter, is situated on this same borderland. Just as allergists no doubt see psychiatric

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symptoms in their allergic patients, we see allergic-like phenomena in ours. We see, as you also do, physical changes induced by psychic stimuli, the exact mechanisms of which are difficult to understand. For example, under deep hypnosis, a suitable patient can be briefly touched with a pencil eraser and told that it is a hot iron and that he must endure the pain. Subsequent to this event, a blister may arise on the touched spot. Typical dermatographia also can be experimentally produced. A patient may be given a cathartic, told that it is constipating, and his body will respond to the suggestion rather than to the drug. Clinically, we see many examples of patients who, while in psychotherapy and in a condition of stress, manifest all the symptoms which you encounter, extending from urticaria to wheezing. We often see that people sensitive in your sense of the word, allergenically sensitive, are sensitive in our sense of the word, i.e., strongly susceptible and responsive to painful states of emotion, frustrations and disappointments in their present and in their past.

So it is not surprising that our two specialties, contiguous—even overlapping as they are in so many areas, should give us both common interests and scientific tasks.

It is possible to outline briefly the psychodynamics of the patient likely to be susceptible to the development of an allergic disorder. Rather than to recapitulate what is known about the specific psychodynamics of each allergic disorder, perhaps it would be more germane to outline briefly some of the origins of stress as they are generally conceived by psychiatrists and the mechanisms, particularly the unconscious ones, by which stresses are handled. This is the one common factor, conscious and unconscious stress, which is found in all neuroses and in all the psycho-physiological illnesses. This, however, necessitates a brief digression, a skeletonized outline of the topography of the mental apparatus.

We know from a variety of evidence that the mind is not wholly subsumed by that part of the psychical apparatus which can be reached by thinking and remembering. Rather, like the one-seventh of the iceberg which shows above the surface of the sea, it is only a small part of a larger whole. This larger part to which we do not have direct access is commonly referred to in psychiatry by the term, the unconscious. But it is important to realize that this shorthand term refers not just to the repository of our repressed wishes, hopes and fears and the storehouse of our early memories. The term also refers to a method of concept formation and thinking that is quite alien to our waking, deliberate ratiocination. It is a process, rather than a place or thing; but to speak allegorically, one might say, it is the little, magical-thinking child within us, preserved timeless and intact. Needless to say, the reasoning of this part of the mind as shown by dreams and other of its products is vastly different from conscious cognition and mentation. It is archaic, primitive, irrational and paleological. Here all the rules of rationality, that most valuable product of learning and experience, go awry. In dreams and in psychoses and in the symbolism of neurotic symptom forma-

tion, we see a wholly different kind of thinking. Here a symbol can be the same as a thing symbolized. Similarity is equated with identity. Opposites can stand for each other. And oddly enough, this magical thinking which is the hallmark of unconscious mental process obeys certain lawful regularities of its own, laws of paleologic or of illogic, one might say, just as rationality obeys laws of formal logic. Hence, this paleological unconscious part of the mind can be studied, understood, predicted, and through the application of this knowledge, modified, ameliorated, controlled and directed.

We know, moreover, that all problems experienced by the human organism impel solution, and the stronger the need or drive, the more powerfully impelling is the problem-solving behavior. All of us have had experience with this phenomenon. What we are likely to forget is that if a wish is alien and unacceptable to our conscious, waking, rational, moral, civilized and disciplined selves, it does not mean that that wish ceases to exist. To employ a simile, it merely goes underground; it is repressed. And this process, repression, is an unwitting, automatic, unconscious submersion of the forbidden impulse, in contradistinction to suppression which is a deliberate, conscious frustration of it. For example, if we are angry and are aware of it, but deliberately check it, the emotion is handled quite differently than if it is so consciously unacceptable that it is automatically repressed. If rage is repressed, there is no conscious emotion of anger, but we do see and can measure the physiological and biochemical concomitants of it.

The important point to make here is that we fool only the mind, not the body. The body, which is in communication with these lower cerebral centers, responds as though we were angry, or afraid, or guilty, or sexually excited. The individual is only consciously aware of the pounding of the heart, the sweating of the palms, the twitching of his muscles, the tension of muscular contraction, and is wholly unable to account for these phenomena, which are frightening and perplexing to him. We can indeed reproduce these phenomena experimentally. A frightening circumstance can be suggested to a patient hypnotically and then the conscious awareness of the fright erased from his mind, but the body still knows; the heart pounds, the muscles are tense, the body sweats, and all this puzzles and disconcerts the subject, who cannot see why he should be reacting so and accounts for it by rationalizations, saying that perhaps he is in a draft or perhaps it is the cauliflower he ate for dinner or a recent attack of virus, et cetera. When the conscious awareness of his repressed fear is restored to him, the physiological concomitants disappear. And this, vastly over-simplified, is one of the goals and methods of intensive insight psychotherapy, to make conscious that which previously had been unconscious—to enable the patient to bring to bear upon his difficulties a completely new set of mechanisms to solve them; namely, his conscious, rational mind. In analogy, if one is locked in a dark room with an enemy, no amount of courage alone will avail. He can only lash out blindly in the darkness at something he can neither see nor understand. If, on the other hand, light is brought into the room he can, with his

conscious, rational mind, perceive the difficulty and use his rational power to take appropriate steps to solve it.

Hence, most physical symptoms of a psychosomatic character are related to the repression of drives and the affects or emotions associated with them. In addition, the paleological portion of our mind often utilizes these symptoms as a symbolic fulfillment of a wish, or a protection against such a fulfillment, or a self-punitive assuagement of guilt. Such symptoms have a valued utility of their own in aiding a compromise between the forbidden wish and the defense against, or punishment of, that wish. As an example, I recall a woman who had a vesicular urticaria limited to the volar surface of the index finger of the left hand. It was discovered that this had been the finger which she had employed in masturbation, which was for her a very ego-alien act. As this became conscious, the vesiculation completely cleared within the space of two days. Another patient would develop severe asthmatic symptoms, largely in the late evenings and most frequently on Tuesdays. It developed that his mother, toward whom he had a deeply repressed feeling of hatred, had died on a Tuesday evening about dark. The memory of this and her edematous death rattles, which he was vicariously repeating in expiation, had been completely repressed until they were extirpated in psychotherapy. This was followed by a complete cessation of the asthma, and after four years it has not returned.

These, of course, are examples of simple dynamisms. Few cases are so orderly, but they serve as examples of the process of symbolic symptom choice. Anxiety is a nameless dread. When it becomes consciously identified and labeled, it is transferred into a fear or a conscious concern, a completely different emotion and one handled differently (both intrapsychically and physiologically) from its predecessor of dread.

What, then, are the effects on the body (we shall exempt the mind here as not being relevant to this purview) of a state of chronic and enduring fear? Fortunately, we are not limited to clinical impressions for an answer to this question. A vast amount of experimental evidence is available. If an animal is kept in a state of dread for a lengthy and indefinite period of time, Selye's adaptational syndrome is produced which leads to all the stress allergies and even to death. We find also that the animal's tissues will become hypersensitive to a variety of drugs and chemicals to which he was not previously sensitive, and that this sensitivity will in part continue after the ostensible causes of the stress have been removed. His tissues react to new stimuli with the same hypersensitivity as does sunburned skin; in other words, one can produce a sensitive animal, both from the psychiatric point of view and from an allergic point of view, by experimental design.

In an animal, however, this sensitivity will be almost wholly extinguished when the environmental conditions causing it have been removed. With the sensitivity of our patients, however, it is unfortunately not so simple. We have seen examples of this. We send the nervous, tense patient to the mountains or the seashore and tell him to get a good rest and he will feel

better. Instead, he takes his conflicts with him and becomes worse. Stress in human beings, unlike animals, becomes symbolically extended and perpetuated, and so relief from the environment alone is rarely curative. In addition, the state of chronic stress appears to be much more resistant to extinction when the causes for the dread, terror and anxiety are not accessible to one's conscious, rational, thinking, remembering mind. Nameless terror is infinitely more disorganizing than discrete fear. Also, unlike the animal, man is a conceptualizing organism whose sources of tension and frustration are very complexly produced and hence are rarely handled by simple advice, counsel or environmental manipulation. It is just this state of chronic stress, largely unconsciously produced and perpetuated, which, in my opinion, is the ubiquitous concomitant of all neurotic, psychotic, and psychosomatically ill persons.

Perhaps it is appropriate to ask: Are there any common psychological antecedents which are likely to inaugurate and perpetuate this condition of stress potentiation? In a word, no. There is none which is universal. There is a wide variety of situations and conflicts in childhood and adulthood which may be related. These may involve needs as widely varied as the need for identity, for personal adequacy, for security, sexual gratification, et cetera. There is one prominent antecedent familial situation, however, which we commonly encounter in persons who are allergenically sensitive. I refer to early, persistent, covert parental rejection, a rejection experienced fairly continuously, rather than sporadically, in the patient's early life. This factor, as a stress inducer, appears to operate somewhat in the following manner.

We know that a child, owing to the prelogical state of his development, is largely unable to form any logical concept of himself as a worthy or adequate person. Instead, he absorbs, so to speak, *in toto,* the views held towards him by the parents, or rather the unconscious views held towards him by the parents, since he is quite unwittingly perceptive of, and responsive to, these parental views concerning him. Hence, if the individual is consistently deprived or rejected by parents who insist and aver to him, and perhaps even to themselves, that they love him, a deep and persistent conflict state is induced. He identifies with that part of his parents which covertly tells him that he is evil, bad, unworthy, inadequate; and the unconscious representation of this loving and approving parental image is very resistant to later environmental change and relearning. The conception that the parents are unloving usually, however, has to be repressed, since this evokes guilt, depression, and raging hostility towards them which are incompatible with the developing morality of the individual. This results in certain psychological characteristics. We might superficially characterize the result of such a childhood and environment as showing a deep need for affection and support, little capacity to give this to others, a massive repression of all emotions, particularly sadness and rage, and numerous sexual inhibitions and problems; and in my experience most persons prone to allergic sensitivity have a background similar to this.

It is important to make the point, however, that this is a common pattern, not an exclusive one. The human psyche is infinitely complex, and there are multiple and interlocking sources of unconscious conflict. The one described is a very common one in my experience and often encountered. It is by no means universal.

As Dr. Edward Weiss is fond of saying, "The psychosomatic approach means not that you study the soma less, but that you study the psyche more." It means to be more the physician and less the doctor. It means to include in our histories an interest and concern for the psychological events of the patient's life as well as the medical ones, and to know reasonably well the kinds of life situations which in human existence induce and foster conflict. It means that as physicians we are committed to the scrutiny of and treatment of the whole person. None of us can exempt ourselves from the responsibility of learning the interview techniques and the techniques of simple psychotherapy which will enable us to ameliorate the patient's physical and psychical ills and to identify his more serious psychological problems. We should be able to refer patients without undue conflict for the more necessary intensive help.

If this capability of ministering to both kinds of the patient's needs, somatic and psychic, is a desideratum for most specialists, it is surely a necessity for the successful practice of allergy. I have been surprised to note how often the allergists who, I find, do good work resemble the "old family doctor." Like him, they are masters of that fine art of fostering and encouraging warm, reassuring relationships with their patients. They know how to communicate and to encourage communication with others. They know much about life and its vicissitudes, deviations and complexities, and are skillful in helping their patients to see the relationships between stress, worry and physical illness. They can assist them to identify and remove exogenous sources of stress. They foster and encourage confidence and scrupulously keep a patient's confidences. When referral for any medical or psychological reason is indicated, they do this without frightening the patient, without punishing him, or without abandoning him. In short, some of the finest all-round medicine I have seen has been practiced by allergists. I hope that the years ahead result in an ever closer interaction and cooperation between our two specialties.

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STUDIES IN ALLERGY

I. The Specific Activity of Pollen Oil

Historical Document

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IT IS WELL recognized that substances of a nonprotein nature may be the specific excitants of hypersensitive reaction in man. Cooke in 1919 reported fifteen cases of aspirin sensitivity. Coca believes that the specific allergen in the watery extracts of pollen, and the possibility that the oil present in pollen might also act as a specific allergen has apparently been overlooked.

This preliminary report will record the observations made with the oil of ragweed pollen and certain other oils.

Experiment I.—Oil was removed from dry ragweed pollen with the usual fat solvents such as toluol, carbon tetrachloride, ethyl ether and petroleum ether. The extraction may be carried out either by washing the pollen in a Seitz filter with reduced pressure, or preferably in a Soxhlet apparatus. In both procedures, using the solvents mentioned, about 12 per cent by weight of pollen is removed. After evaporation of the solvent, the residue is dark, greenish-brown in color with semisolid oily consistency. In every case before testing, the oil was redissolved in a specially prepared water free solvent to exclude all water soluble material and filtered through a Seitz filter to remove pollen granules mechanically present in the oil. Qualitative chemical tests showed absence of nitrogen and phosphorus.

Tests were made with the pure oil by the scratch method. Intradermal tests were made with a suspension of oil in 1 per cent alcoholic saline solution. Control tests were made with timothy pollen oil and cottonseed oil purified and prepared the same way.

Thirty cases with a clinical history of autumnal hay fever and found sensitive to the watery extract of ragweed pollen were tested with the oil by the scratch and intradermal method. About two-thirds of them gave positive immediate skin reactions of the characteristic urticarial type. All were negative to the watery extracts of timothy pollen and cottonseed and to the oil of timothy pollen and cottonseed. Serum from the oil sensitive cases in this group was used for passive transfer of sensitization by the method of Prausnitz and Küster. Sensitized sites gave positive reactions, and control sites were negative.

Experiment II.—Olive oil, glycerin and petroleum were added to ragweed pollen. After standing for six hours it was separated, filtered through a Seitz filter and tested. Positive reactions were obtained on ragweed sensitive cases. As a control, olive oil, glycerin and petrolatum were added to ragweed pollen from which all oil had been removed. After extracting

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for seven days, the solvents were filtered and tested. Reactions on ragweed sensitive cases were negative. This experiment seems to show that the allergen is naturally present in the oil and that the positive skin reactions were not due to traces of water soluble allergens.

Experiment III.—Ragweed pollen oil was taken up in petroleum ether and thoroughly washed with a small amount of saline which was then separated. Three such successive washings were done, and the saline was separately saved and filtered for testing. Positive reactions of slight degree and equal intensity were obtained with each of the three successive washings. The oil recovered after the washings showed no appreciable change in its reactions. If the active substance in the oil was really water soluble, undoubtedly the saline washings would have shown more intense reactions, and the first washing would have been more active than the second or third. The presence of such slight reactions in the saline washings can best be explained by a slight solubility of the oil in water.

Experiment IV.—Oil was extracted from the separate pollens of the two prevalent varieties of ragweed—*trifida* and *artemisiaefolia*. Tests by intradermal and scratch methods on fifteen clinical cases, which had proved sensitive to watery extract, showed the same reactions to the two oils and bear out the former observations on the biologic identity of the two ragweed pollens.

Additional facts have been elicited as follows: Ragweed pollen oil apparently remains fully active after eight months at room temperature, and its activity is not impaired by heating at 125° C for one-half hour. Oils extracted from horse and dog dander, orris, wheat and walnut have so far been negative in the few specifically sensitive cases tested. The oil of timothy pollen is specifically active in certain cases of early hay fever sensitive to the watery extract of this pollen.

It was noted in some of the cases tested with oil of ragweed pollen that a dermatitis developed at the test site five to twenty-one days later. This is probably the same reaction as that observed by Cooke* in clinical cases of seasonal dermatitis. His cases were found to react to the absolute alcohol extract of the dried leaf of the ragweed plant. He regards these cases as similar to dermatitis venenata.

SUMMARY

An important question arises as to whether the active substance in the oil is identical in its biologic reactions with that in the water extract of pollen. The fact that but two-thirds of the cases reactive to watery extract react also to oil indicates either a quantitative or a qualitative difference in the active substance of the two extracts.

Tests on passively sensitized areas of skin in normal cases have shown activity to water extract when these sites had been exhausted by the oil extract. Further experiments along these lines are being done.

*Personal communication.

President's Letter

Recently, it was my pleasure to visit the Statler Hilton in Dallas, the site of our convention for 1961. The physical facilities there are suited ideally for our needs. The hotel is adjacent to the down-town shopping area. The management is most cooperative, and I feel sure that our stay in Dallas will be delightful and intellectually profitable.

The Graduate Instructional Course has been completed and is excellent. There is room for a few more papers in the general scientific session of the Congress. Associates of the College are encouraged to submit manuscripts to be presented in competition for the Bela Schick Award. The Program Committee would like to have some studies on any aspect of allergy prepared by an intern or resident submitted for consideration for the Clemens von Pirquet Award. These prizes are offered each year by the Women's Auxiliary.

All manuscripts (or 250-300 word abstracts of them) for consideration in any of the above categories must be submitted in quadruplicate to the over-all program chairman, Dr. Philip M. Gottlieb of Philadelphia. The deadline for the receipt of such abstracts has been extended to December 15, 1960. To qualify for an award, the author must present his paper in person at the convention.

Some space is still available to those who wish to present a scientific exhibit. The abstract of your material should be submitted to Dr. Gottlieb before January 15, 1961. Booths will be assigned in the order in which acceptable exhibits are received.

Your officers appreciate the cooperation of all members of the College in their efforts to make our 1961 convention superior in every detail.

GILES A. KOELSCHE, M.D.

President, The American College of Allergists

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